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IN THE UNITED STATES PATENT
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Patentees: Erik H. F. Wong et al.
Patent No. 6,465,458 B1
Issued: October 15, 2002
Title: METHOD FOR TREATING
OR PREVENTING
CHRONIC PAIN WITH A
HIGHLY SELECTIVE
NOREPINEPHRINE
REUPTAKE INHIBITOR
Examiner: William R. A. Jarvis
Group Art Unit: 1614
Attorney Docket No.: 28341/6248.4

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) P.O. Box 1450, Alexandria, Virginia
) 22313-1450, on March 17, 2005.

Sandip H. Patel (Reg. No. 43,848)
Attorney for Patentees/Assignee

PATENT OWNER CITATION OF PRIOR ART
PURSUANT TO 35 USC § 301 AND 37 CFR 1.501(a)

Commissioner for Patents
P.O. Box 1450
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WILLIAM R. DIXON, JR.
SPECIAL PROGRAM EXAMINER
4/4/05

Dear Sir:

The above-captioned patent is assigned to Pharmacia & Upjohn Company by virtue of an assignment recorded at the U.S. Patent and Trademark Office (the "PTO") on September 26, 2000, at Reel 010988 and Frame 0398. This paper and the publications identified herein are being submitted on behalf of the assignee and in accordance with 35 USC § 301 and 37 CFR § 1.501(a). This paper also is being submitted in view of a recommendation made by Kenneth M. Schor of the PTO's Office of Legal Administration during a telephone conference with undersigned attorney on February 16, 2005.

On November 22, 2004, the assignee filed a request for ex parte reexamination of the '458 patent (Reexamination Control No. 90/007,313) in which it identified the publications enumerated in the appendix attached hereto. Copies of the publications are submitted herewith as they could possibly be considered by the PTO to have a bearing on the patentability of the claims of the '458 patent. The first four listed publications are collectively referred to herein as the "Murdock publications." The fifth and sixth listed publications are referred to herein as the "Leonard book" and the "Healy publication," respectively.

The request included a table listing each claim for which reexamination was sought along with an identification of the potentially-relevant disclosure in the Murdock publications,

the Leonard book, and the Healy publication. For the sake of brevity herein, the request indicated that the four Murdock publications disclose a transdermal composition containing racemic reboxetine and administration of the same to a human being to treat pain, including chronic pain. The request also indicated that the Healy publication and Leonard book merely speculate that norepinephrine reuptake inhibitors are likely to be useful for treating pain syndromes. The request was filed on a belief that the foregoing disclosures may possibly be considered by the PTO to raise a substantial new question of the patentability of claim 1 of the '458 patent.

Notwithstanding the disclosure in the four Murdock publications, the Leonard book, and the Healy publication, the request clearly indicated that, for reasons already of record during prosecution of the '458 patent, none of the publications anticipates any claim of the '458 patent under 35 USC § 102, and none of the publications renders any claim of the '458 patent obvious under 35 USC § 103 either alone or in combination with any other publication. The publications do not disclose or suggest a method of treating an individual suffering from chronic pain, wherein the method includes the step of administering to the individual a therapeutically effective amount of a composition comprising an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, as recited in the claims of the '458 patent. Thus, while the disclosure in the publications may possibly be considered by the PTO to raise a substantial, new question of patentability, the disclosure neither anticipates nor renders obvious any of the '458 patent claims.

On February 7, 2005, the PTO issued a decision denying the request for ex parte reexamination. The decision, however, erroneously states that the "request indicates the Requestor [sic] considers that Claims 1-32 of [the '458 patent] are unpatentable over" the four Murdock publications, the Leonard book, and the Healy publication. No such indications are present in the request. Notwithstanding these erroneous statements, the decision indicates that the references set forth in the request were considered, but fail to raise a substantial new question of patentability as to any claims of the '458 patent. The assignee agrees with the conclusion reached by the PTO that all of the claims of the '458 patent are patentable.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP

March 17, 2005

By:


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APPENDIX

Accompanying this paper are copies of the following publications:

- A. Murdock et al. International Publication No. WO 00/00120.
- B. Murdock et al. U.S. Patent No. 6,479,074 B2.
- C. Murdock et al. U.S. Patent No. 6,572,880 B2.
- D. Murdock et al. U.S. patent application publication No. 2002/0015713 A1.
- E. Leonard et al., "The Differential Effects of Antidepressants," pgs. 42, 64-72, and 81-89 (Martin Dunitz & Co., London, 1999).
- F. Healy et al. (1998) J. Affective Disorders 51:313-322.
- G. Murdock et al. U.S. Patent No. 6,290,986 B1.
- H. International Publication No. WO 99/11208.
- I. International Publication No. WO 01/47503.
- J. International Publication No. WO 01/62236.
- K. M. Mucci, "Reboxetine: A Review of Antidepressant Tolerability," Journal of Psychopharmacology, Oxford University Press, 11(4):533-537 Supp, 1997.
- L. Search Report in counterpart EP 04013383.7-2123, dated July 22, 2004 (4 pages).
- M. Search Report in counterpart EP 04013382.9-2123, dated July 22, 2004 (4 pages).



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60/122,903	05 March 1999 (05.03.1999)	US

(60) Parent Application or Grant

PHARMACEUTICALS APPLICATIONS ASSOCIATES, LLC
[/]; (). MURDOCK, Robert, W. [/]; (). WILLIAMS, C.,
Donald [/]; (). MURDOCK, Robert, W. [/]; (). WILLIAMS,
C., Donald [/]; (). MANDRAGOURAS, Amy, E. ; ().

Published

(54) Title: METHODS AND TRANSDERMAL COMPOSITIONS FOR PAIN RELIEF

(54) Titre: COMPOSITIONS ANTALGIQUES TRANSDERMIQUES ET LEURS METHODES D'ADMINISTRATION

(57) Abstract

The present invention features methods and compositions for transdermal administration. In one embodiment, the invention features methods and compositions for transdermal administration of an amine containing compound having biphasic solubility and/or agent which enhances the activity of the amine containing compound having biphasic solubility, e.g., a muscle relaxant, to relieve pain.

(57) Abrégé

La présente invention concerne des compositions antalgiques transdermiques et leurs méthodes d'administration. Selon un mode de réalisation, l'invention concerne des compositions à administration transdermique qui renferment un composé avec amine à solubilité biphasique et/ou un agent qui favorise l'activité antalgique dudit composé en tant que décontractant musculaire.

CORRECTED
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: A61F 13/02	A1	(11) International Publication Number: WO 00/00120 (43) International Publication Date: 6 January 2000 (06.01.00)
(21) International Application Number: PCT/US99/14653 (22) International Filing Date: 29 June 1999 (29.06.99) (30) Priority Data: 09/106,684 29 June 1998 (29.06.98) US 60/122,903 5 March 1999 (05.03.99) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications US 09/106,684 (CIP) Filed on 29 June 1998 (29.06.98) US 60/122,903 (CIP) Filed on 5 March 1999 (05.03.99) (71) Applicant (for all designated States except US): PRAECIS PHARMACEUTICALS INCORPORATED [US/US]; One Hampshire Street, Cambridge, MA 02139 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): MURDOCK, Robert, W. [US/US]; 651 Ames Road, Selah, WA 98942 (US). WILLIAMS, C., Donald [US/US]; 311 North 22nd Avenue, Yakima, WA 98902 (US).		(74) Agents: MANDRAGOURAS, Amy, E. et al.; Lahive & Cockfield, LLP, 28 State Street, Boston, MA 02109 (US). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: METHODS AND TRANSDERMAL COMPOSITIONS FOR PAIN RELIEF (57) Abstract <p>The present invention features methods and compositions for transdermal administration. In one embodiment, the invention features methods and compositions for transdermal administration of an amine containing compound having biphasic solubility and/or agent which enhances the activity of the amine containing compound having biphasic solubility, e.g., a muscle relaxant, to relieve pain.</p>		

* (Referred to in PCT Gazette No. 13/2000, Section II)

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Description

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METHODS AND TRANSDERMAL COMPOSITIONS FOR PAIN RELIEF*Field Of The Invention*

The present invention is directed to methods and compositions for transdermal administration. In particular, the present invention is directed to methods and compositions for the transdermal administration of an amine containing compound having biphasic solubility and/or an agent which enhances the activity of the amine containing compound having biphasic solubility, e.g., a muscle relaxant, to relieve pain.

Background Of The Invention

It is believed that damage to somatic sensory nerves causes a somatic sensory loss. Such damage can be caused by a variety of means including trauma, diseases such as diabetes, herpes zoster and late-stage cancer, chemotherapy, or by a chemical injury. It is believed that neural pain circuits rewire themselves, both anatomically and biochemically, after nerve injury. In many patients suffering from damage to somatic sensory nerves, negative symptoms such as numbness are joined by positive sensations, involving a sort of false sensation of pain. The experience can range from mild dysesthesia to excruciating pain, rendering some patients unable to work, walk or do other daily activities.

In the past, patients were generally treated by administration of analgesics to relieve pain. A vast majority of such patients receive doses of these agents orally. Unfortunately, in some situations, oral administration of such agents has been associated with a variety of side effects, such as liver damage, kidney damage, gastrointestinal side effects, addiction, sedation, and/or weight gain which cannot be tolerated well by the patient. In other cases, malabsorption of oral preparations have resulted in subtherapeutic plasma levels. In other cases, the agents have relatively short plasma half-lives, necessitating inconveniently frequent dosing. In general, oral delivery involves a time delay as the analgesic is absorbed via the digestive system before entering the bloodstream. A number of agents which have traditionally been administered orally or by injection have been inappropriate or suboptimal for some patients when so-administered. There are a number of medications which, in at least some patients, are not tolerated well when orally administered (e.g. which cause undesirable gastrointestinal or other side effects) and/or which provide undesirably high or low concentrations or delayed concentrations in a target tissue. In some cases, dosages which are appropriate for oral administration, upon being distributed more or less uniformly throughout the body, are undesirably low in a particular area, e.g., tissue, to achieve desired results. Oral or injection administration may result in too slow or too rapid increase in blood plasma levels, e.g., may involve an undesirably long time delay

5 as the analgesic is absorbed by the digestive system before entering the bloodstream, or
may result in a "spike" in blood plasma levels followed by an undesirably low level,
where a more constant level would be preferable. Some analgesics are particularly
prone to cause or contribute to kidney or liver damage when administered orally.

10 5 Although other forms of delivery of pharmaceuticals agents are known, each has
its drawbacks. Parenteral (i.e., intravenously or intramuscularly injected) administration
is inconvenient and expensive, and is rarely used outside the hospital. Inhalation is
believed to be not feasible with many analgesic agents currently in use.

15 Therefore, there is a need for an analgesic delivery system which provides effective and
10 acceptable levels, while preferably avoiding or reducing undesired effects such as liver
damage or gastrointestinal side effects.

20 *Summary Of The Invention*

15 The present invention provides a transdermal composition for the treatment of
pain in a subject, particularly a human subject. The transdermal composition for the
treatment of pain in a subject includes an amine containing compound having biphasic
25 solubility in an amount effective to treat pain in a subject and a pharmaceutically
acceptable carrier suitable for transdermal delivery of the amine containing compound,
e.g., a lecithin organogel carrier. In a preferred embodiment, the transdermal
20 composition further includes an agent which enhances the activity of the amine
containing compound having biphasic solubility, e.g., a muscle relaxant, such as
30 guaifenesin, chlorzoxazone, dantrolene sodium, metaxalone, carisoprodol, and
combinations thereof. Preferably, the agent which enhances the activity of the amine
containing compound having biphasic solubility, e.g., the muscle relaxant, also has a
25 biphasic solubility.

35 In one embodiment of the present invention, the amine containing compound
having biphasic solubility is an antidepressant compound, such as a tricyclic
antidepressant compound, e.g., doxepin or trimipramine.

40 In another embodiment of the present invention, the amine containing compound
30 having biphasic solubility is a sodium channel blocker, an anti-epileptic compound, or
an anti-convulsant compound.

45 Another embodiment of the invention features a transdermal composition which
includes an amine-containing compound as described herein and an anti-inflammatory
compound, such as a nonsteroidal anti-inflammatory compound, e.g., celecoxib,
35 etodolac, mefenamic acid, nabumetone, salsalate, naproxen, vioxx[®], and combinations
thereof. Such a composition can further include an agent which enhances the activity of
the amine containing compound, e.g., a muscle relaxant such as guaifenesin.

5 In another aspect, the invention features a transdermal composition for the treatment of pain in a subject including an amine containing compound having biphasic solubility in an amount effective to treat pain in a subject; a muscle relaxant in an amount effective to enhance the activity of the amine containing compound having
10 5 biphasic solubility; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound having biphasic solubility and the muscle relaxant.

15 In yet another aspect, the invention features a transdermal composition for the treatment of pain in a subject including doxepin in an amount effective to treat pain in a subject; guaifenesin in an amount effective to enhance the activity of doxepin; and a
20 10 pharmaceutically acceptable carrier suitable for transdermal delivery of the doxepin and the guaifenesin.

25 Other aspects of the invention feature methods for treating pain in a subject in which the subject is contacted with a transdermal composition including an amine containing compound having biphasic solubility in an amount effective to treat pain in the subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound to thereby treat pain in the subject. In a preferred
30 15 embodiment, the transdermal composition is applied to the skin of the subject.

35 Another aspect of the invention features a method for selecting a compound suitable for treating pain in a subject. The method includes transdermally administering an amine containing compound having biphasic solubility to a subject; and determining whether pain is treated in the subject to thereby select a compound suitable for treating pain in a subject. In a preferred embodiment, the method can further include modeling the compound using a computer equipped with a three-dimensional chemical structure
40 20 modeling program; and determining whether the three-dimensional chemical structure of the compound possesses sufficient characteristics to be useful as a sodium channel blocker, thereby selecting a compound suitable for treating pain in a subject.

45 In another aspect, the invention features a transdermal composition suitable for transdermal delivery, which includes a therapeutically effective amount of a
50 30 pharmaceutical compound (e.g., a serotonin specific reuptake inhibitor, a mood stabilizing compound, a dopamine compound, a compound suitable for treating attention deficit hyperactivity disorder, a compound suitable for treating hypertension and akathisia, an analgesic compound, or a compound used in the treatment of impotence) and a pharmaceutically acceptable carrier suitable for transdermal delivery of the
55 35 pharmaceutical compound, e.g., a lecithin organogel carrier.

In yet another aspect, the invention features a transdermal composition for treatment of pain in a subject which includes a compound capable of blocking afferent neuron transmission in an amount effective to block afferent neuron transmission in a

5 subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the compound.

10 Other features and advantages of the invention will be apparent from the following detailed description and claims.

Brief Description Of The Drawings

15 *Figure 1* is an evaluation form used in evaluating an embodiment of the present invention.

20 *Figure 2* is a table depicting the results from clinical experiments using compositions of the invention.

Detailed Description Of The Invention

25 The present invention provides a transdermal composition suitable for treatment of pain in a subject. The transdermal composition includes an amine containing compound having biphasic solubility in an amount effective to treat pain in a subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound having biphasic solubility.

30 As used herein, the term "subject" includes a mammal, such as a human, a horse, a pig, a cow, a mouse, a rat, a rabbit, or a goat. In preferred embodiment, the subject is a human.

35 As used herein, the term "pain" is art recognized and includes a bodily sensation elicited by noxious chemical, mechanical, or thermal stimuli, in a subject, e.g., a mammal such as a human. The term "pain" includes chronic pain, such as lower back pain; pain due to arthritis, e.g., osteoarthritis; joint pain, e.g., knee pain or carpal tunnel syndrome; myofascial pain, and neuropathic pain. The term "pain" further includes acute pain, such as pain associated with muscle strains and sprains; tooth pain; headaches; pain associated with surgery; or pain associated with various forms of tissue injury, e.g., inflammation, infection, and ischemia.

40 As used herein, the term "amine containing compound having biphasic solubility" includes compounds having at least one amine moiety and having sufficient lipid solubility (e.g., solubility in polar solvents such as ethanol, ethoxydiglycerol, ethoxydiglycol, chloroform, benzene, and the like) such that the compound passes through the stratum corneum, and has sufficient aqueous solubility to be active in the aqueous environment of the dermis and the underlying tissue.

50 Transdermal compositions of the present invention include an amine containing compound having biphasic solubility in an amount effective to treat pain in a subject.

5 As used herein, the terms "amount effective to treat pain in a subject" and "effective
amount" are used interchangeably herein and include an amount effective, at dosages
and for periods of time necessary, to achieve the desired result, e.g., sufficient to treat
pain in a subject. An effective amount of an amine containing compound or a
10 5 pharmaceutical compound as defined herein may vary according to factors such as the
disease state, age, and weight of the subject, and the ability of the amine containing
compound or pharmaceutical compound to elicit a desired response in the subject.
Dosage regimens may be adjusted to provide the optimum therapeutic response. An
15 effective amount is also one in which any toxic or detrimental effects of the amine
20 10 containing compound having biphasic solubility or pharmaceutical compound are
outweighed by the therapeutically beneficial effects.

The transdermal compositions of the invention can further include an agent
which enhances the activity of the amine containing compound having biphasic
20 solubility. As used herein, an "agent which enhances the activity of the amine
15 containing compound having biphasic solubility" includes an agent which enhances the
pharmacological activity of the amine containing compound having biphasic solubility
(e.g., the ability of the amine containing compound to treat pain), or enhances the
25 transdermal delivery of the amine containing compound having biphasic solubility (e.g.,
the ability of the amine containing compound to cross the stratum corneum), or
20 enhances both the pharmacological activity and the transdermal delivery of the amine
containing compound. Examples of agents which enhance the activity of the amine
30 containing compound having biphasic solubility, include muscle relaxants, described in
further detail below.

As used herein, the term "transdermal" composition includes compositions
25 capable of passing through the stratum corneum of a subject. The term transdermal
35 further includes compositions capable of passing through the epidermis of a subject,
compositions capable of passing through the dermis of a subject, and compositions
capable of passing through the hypodermis of a subject. In preferred embodiments, the
term transdermal includes compositions capable of passing through the skin of a subject
40 and reaching the underlying tissues and organs.

As used herein, the term "transdermal delivery" includes delivery of, for
example, a compound through the stratum corneum of a subject. The term transdermal
45 delivery further includes delivery of, for example, a compound through the epidermis of
a subject, delivery of, for example, a compound through the dermis of a subject, and
35 delivery of, for example, a compound through the hypodermis of a subject. In preferred
embodiments, the term transdermal delivery includes delivery of, for example, a
compound through the skin of a subject to the underlying tissues and organs.

5 The present invention further features a transdermal composition for treatment of pain in a subject which includes a compound capable of blocking afferent neuron transmission in an amount effective to block afferent neuron transmission in a subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the
10 5 compound.

As used herein, the term "compound capable of blocking afferent neuron transmission" includes a compound which is capable of blocking the ability of an afferent neuron, i.e., a sensory neuron, to carry an impulse toward the central nervous system.
15 10

Various aspects of the invention are described in further detail in the following subsections:
20

Amine Containing Compounds Having Biphasic Solubility

15 Amine containing compounds having biphasic solubility for use in the transdermal compositions of the invention include antidepressant compounds, antiepileptic compounds, anticonvulsant compounds, and sodium channel blockers.
25 As used herein, the term "antidepressant compounds" includes compounds capable of alleviating the symptoms of depression. Examples of antidepressant compounds include all tricyclic antidepressants (e.g., amitriptyline, dothiepin, or lofepramine), bupropion (sold under the trade name Wellbutrin), reboxetine (sold under the trade name Edronax), ncfazodone (sold under the trade name Serzone) and trazodone (sold under the trade name Desyrel). Antidepressant compounds are described in, for example, the 1998 SIGMA catalogue and the "The Merck Index", 12th Ed., Budavari *et al.*, eds., Merck & Co., Inc., Rahway, N.J., 1996, the contents of which are incorporated herein by
30 35 reference.

In one embodiment of the present invention, the antidepressant compounds of the present invention contain a tricyclic moiety. Therefore, in a preferred embodiment, a transdermal composition of the present invention includes a tricyclic antidepressant
40 30 compounds. Exemplary tricyclic antidepressants include adinazolam, amitriptylinoxide, amoxapine, clomipramine, demexiptiline, dimetacrine, dothiepin, doxepin, imipramine N-oxide, iprindole, lofepramine, melitracen, metapramine, noxiptilin, pizotyline, propizepine, quinupramine, tianeptine, and trimipramine. A particularly preferred tricyclic antidepressant for use in the compositions of the invention is doxepin.
45

35 Tricyclic antidepressant compounds are described in, for example, "Guide to Clinical Neurology" by J.P. Mohr *et al.* (Churchill Livingstone, 1995), the contents of which are incorporated herein by reference.
50 55

5 Preferably, the tricyclic antidepressant compound is selected from the group consisting of doxepin, trimipramine, other tricyclics having biphasic solubility, and combinations thereof. When combined with other compounds, such as an agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant, and/or
10 5 an anti-inflammatory compound, e.g., a nonsteroidal anti-inflammatory compound, as discussed below, the tricyclic antidepressant preferably constitutes from about 1 % by weight (% by wt.) to about 30 % by wt. of the total amount of the pharmaceutical, more preferably from about 3 % by wt. to about 15 % by wt., and most preferably from about
15 5 % by wt. to about 13 % by wt.

10 The amine containing compounds having biphasic solubility used in the transdermal compositions of the invention further include antiepileptic compounds. As used herein, the term "antiepileptic compound" includes compounds capable of alleviating the symptoms of epilepsy. Exemplary antiepileptic compounds for use in the compounds of the invention include lamotrigine, felbamate, and carbamazepine.

15 Preferably, the antiepileptic compound is selected from the group consisting of lamotrigine, felbamate, carbamazepine, and combinations thereof. When combined with other compounds, such as an agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant, and/or an anti-inflammatory compound, e.g., a nonsteroidal anti-inflammatory compound as discussed below, the antiepileptic
20 15 compound constitutes from about 1 % by wt. to about 30 % by wt. of the total amount of the pharmaceutical, more preferably from about 3 % by wt. to about 20 % by wt., and most preferably from about 5 % by wt. to about 15 % by wt. Antiepileptic compounds are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th
30 20 Ed., Budavari *et al.*, eds., Merck & Co., Inc., Rahway, N.J., 1996, and the "Guide to Clinical Neurology" by J.P. Mohr *et al.* (Churchill Livingstone, 1995) the contents of
35 25 which are incorporated herein by reference.

In another aspect of the present invention, the amine containing compounds having biphasic solubility of the present invention include anticonvulsant compounds. As used herein, the term "anticonvulsant compound" includes compounds capable of
40 30 alleviating the symptoms of convulsion, i.e., the violent involuntary tetanic contractions of an entire group of muscles. Exemplary anticonvulsant compounds which for use in the compositions of the invention include felbamate, lamotrigine and carbamazepine. Preferably, the anticonvulsant compound is selected from the group consisting of
45 35 felbamate, lamotrigine, and combinations thereof. When combined with other compounds, such as an agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant, and/or an anti-inflammatory compound, e.g., a nonsteroidal anti-inflammatory compound as discussed below, the anticonvulsant
50 40 compound constitutes from about 1 % by wt. to about 30 % by wt. of the total amount of

5 the pharmaceutical, more preferably from about 3 % by wt. to about 20 % by wt., and
most preferably from about 5 % by wt. to about 15 % by wt. Anticonvulsant
compounds are described in, for example, the 1998 SIGMA catalogue, the "The Merck
Index", 12th Ed., Budavari *et al.*, eds., Merck & Co., Inc., Rahway, N.J., 1996, and the
10 5 "Guide to Clinical Neurology" by J.P. Mohr *et al.* (Churchill Livingstone, 1995) the
contents of which are incorporated herein by reference.

In yet another aspect of the present invention, the amine containing compounds
having biphasic solubility of the present invention include adrenergic agonist
15 compounds. Preferably, the adrenergic agonist compound is tizanidine. When
10 combined with other compounds, such as a muscle relaxant and/or nonsteroidal
anti-inflammatory compound as discussed below, the adrenergic agonist compound
constitutes from about 1 % by wt. to about 30 % by wt. of the total amount of the
pharmaceutical, more preferably from about 3 % by wt. to about 20 % by wt., and most
20 preferably from about 5 % by wt. to about 15 % by wt. Adrenergic agonist compounds
15 are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th
Ed., Budavari *et al.*, eds., Merck & Co., Inc., Rahway, N.J., 1996, and the "Guide to
Clinical Neurology" by J.P. Mohr *et al.* (Churchill Livingstone, 1995) the contents of
25 which are incorporated herein by reference.

The amine containing compounds having biphasic solubility used in the
20 transdermal compositions of the invention further include sodium channel blockers. As
used herein, the term "sodium channel blockers" includes compounds which are
30 capable of blocking the activity of a sodium channel. Examples of sodium channel
blockers include tetrodotoxin, flecainide, disopyramide, and terfenadine. Sodium channel
blockers are described in, for example, the 1998 SIGMA catalogue, the "The Merck
25 Index", 12th Ed., Budavari *et al.*, eds., Merck & Co., Inc., Rahway, N.J., 1996, and the
"Guide to Clinical Neurology" by J.P. Mohr *et al.* (Churchill Livingstone, 1995) the
35 contents of which are incorporated herein by reference.

Whenever nerves are damaged, for example, by trauma, by diseases such as
diabetes, herpes zoster, or late-stage cancer, or by chemical injury (e.g., as an untoward
40 30 consequence of agents including the false-nucleoside anti-HIV pharmaceuticals), neural
pain circuits rewire themselves, anatomically and/or biochemically. Thus, following an
injury, new sodium channels are formed which is believed to constitute the basis for
chronic pain development. Through a similar action in the dorsal root ganglia, chronic
45 regional pain syndromes may develop. Each time one of these sodium channels
35 depolarizes, a nerve impulse originates. Because there are so many sodium channels,
there may be a constant cascade of nerve impulses, causing allodynia, burning
sensations, and/or dysesthesias. It is believed that some chronic pains may be mediated
50 through sodium channels in nerve cells. Thus, it is believed that amine containing

5 compounds having biphasic solubility which can block sodium channels may also be used in the transdermal compositions of the invention.

10 In one embodiment of the invention, the amine moiety of the amine containing compounds having biphasic solubility of the present invention may function similar to a sodium ion upon entry into the sodium channel of a nerve cell membrane. A non-polar moiety, which is preferably present in the amine containing compound having biphasic solubility of the present invention may interact with the nerve cell membrane, perhaps through Van der Waals forces. In such cases, it is believed that the presence of the non-polar moiety prevents or inhibits a complete uptake of the amine containing compound having biphasic solubility through the nerve cell membrane. It is believed that one or more these interactions prevent or reduce the amount and/or the rate of depolarization and ion exchange involved in stimulus conduction, thereby decreasing pain sensation.

20 The amount of an amine containing compound having biphasic solubility useful in relieving pain transdermally may be determined by methods known in the art, and typically ranges from about 1 mg to about 300 mg per subject per dose, preferably from about 5 mg to about 100 mg per subject per dose, and more preferably from about 10 mg to about 50 mg per subject per dose, depending on a variety of factors including the particular amine containing compound having biphasic solubility used, whether the area of transdermal application is the site of action, and the intended size of the site of action. In a preferred embodiment, the amount of an amine containing compound having biphasic solubility useful in relieving pain transdermally, is 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 mg, 150 mg, 200 mg, 250 mg, or 300 mg per subject per dose.

35 Muscle Relaxants

40 Transdermal compositions of the present invention may also include a muscle relaxant. As used herein, the term "muscle relaxant" includes compounds which facilitate or enhance the relaxation of muscles (e.g., provide relief from muscle spasm) and, thus, facilitate or enhance the transdermal delivery of the transdermal compositions of the invention. Exemplary muscle relaxants include both skeletal muscle relaxants and smooth muscle relaxants such as anticholinergics, antispasmodics, bronchodilators, and vasodilators. Muscle relaxants are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th Ed., Budavari *et al.*, eds., Merck & Co., Inc., Rahway, N.J., 1996, pp. THER-1 to THER-28, and the "Guide to Clinical Neurology" by J.P. Mohr *et al.* (Churchill Livingstone, 1995) the contents of which are incorporated herein by reference. Preferably, the muscle relaxant is selected from the group consisting of guaifenesin, benzodiazepines (e.g., clozapine or diazepam),

5 chlorzoxazone, dantrolene sodium, metaxalone, carisoprodol, other muscle relaxants
having biphasic solubility, and combinations thereof. More preferably, the muscle
relaxant is selected from the group consisting of guaifenesin, chlorzoxazone, and
combinations thereof. A preferred muscle relaxant for use in the compositions of the
10 invention is guaifenesin.

5 Preferably the muscle relaxant has biphasic solubility. Preferably the muscle
relaxant, when present in the pharmaceutical composition, constitutes from about 1 %
by wt. to about 30 % by wt. of the total amount of the pharmaceutical, more preferably
15 from about 3 % by wt. to about 20% by wt., and most preferably from about 5 % by wt.
10 to about 15 % by wt.

Anti-Inflammatory Compounds

20 The transdermal compositions of the present invention may also include an
anti-inflammatory compound. As used herein, the term "anti-inflammatory compound"
15 includes a compound which is capable of reducing cell migration, caused by ischemic
and trauma associated events, and therefore reduces edema formation to thereby provide
pain relief. Preferably, the anti-inflammatory compound is a nonsteroidal
25 anti-inflammatory compound (*i. e.*, NTHE) including ketoprofen. Anti-inflammatory
compounds, e.g., NTHEs, are described in, for example, the 1998 SIGMA catalogue, the
20 "The Merck Index", 12th Ed., Budavari *et al.*, eds., Merck & Co., Inc., Rahway, N.J.,
1996, pp. THER-1 to THER-28, and the "Guide to Clinical Neurology" by J.P. Mohr *et al.*
30 (Churchill Livingstone, 1995) the contents of which are incorporated herein by
reference. Preferably, the NTHE is selected from the group consisting of celecoxib,
etodolac, mefenamic acid, nabumetone, salsalate, naproxen, Vioxx®, COX-2 NTHEs
25 having biphasic solubility, and combinations thereof.

35 More preferably, the NTHE is selected from the group consisting of celecoxib,
etodolac, naproxen, COX-2 NTHEs having biphasic solubility, and combinations
thereof. Preferably, the NTHE has biphasic solubility. The NTHE, when present in the
transdermal composition, preferably, constitutes from about 1 % by wt. to about 30 %
40 by wt. of the total amount of the pharmaceutical, more preferably from about 3 % by wt.
30 to about 30 % by wt., and most preferably from about 5 % by wt. to about 30 % by wt.

Dosages

45 The concentration as well as the quantity of the amine containing compounds
35 having biphasic solubility, the agents which enhance the activity of the amine containing
compounds, e.g., the muscle relaxants, and the anti-inflammatory compounds can be
varied independently in order to achieve the desired effect. For example, higher
50 concentrations of the amine containing compounds having biphasic solubility, the

5 muscle relaxants, and the anti-inflammatory compounds contained in a dosage form of
decreased viscosity may result in an analgesic with fast onset and short duration. High
concentrations of the amine containing compounds having biphasic solubility, the
muscle relaxants, and the anti-inflammatory compounds contained in a dosage form of
10 5 increased viscosity may result in potent analgesic with fast onset and long duration.
Low concentrations of the amine containing compounds having biphasic solubility, the
muscle relaxants, and the anti-inflammatory compounds in a dosage form of decreased
viscosity may result in mild analgesic with longer onset and short duration. Low
15 concentrations of the amine containing compounds having biphasic solubility, the
muscle relaxants, and the anti-inflammatory compounds contained in a dosage form of
increased viscosity may have mild analgesic properties with longer onset and longer
duration. The ability to vary the concentration of the amine containing compounds
20 having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds
from very low to high of the total composition, combined with the ability to coat thin
15 (about 0.1 mm) or thick (about 0.5 mm) enables the practitioner of the invention to vary
the dosage of the system as needed for particular level of pain and anatomical sites of
interest. It should be appreciated, however, that onset time as well as duration of
25 analgesic effect of the transdermal composition of the present invention will vary from
subject to subject as well as on the basis of the site of application, and properties of the
amine containing compounds having biphasic solubility, the muscle relaxants, and the
20 anti-inflammatory compounds.

30 Generally, the concentration of the amine containing compounds having biphasic
solubility, the muscle relaxants, and the anti-inflammatory compounds can range, on a
weight basis, from about 1 % to about 30 % of the total composition, preferably from
25 about 3 % to about 20 %, and more preferably from about 5 % to about 15 %.

Pharmaceutically Acceptable Carriers

40 The transdermal compositions of the present invention also includes a
pharmaceutically acceptable carrier which is capable of transdermal delivery of the
amine containing compound having biphasic solubility. As used herein, the term
30 "pharmaceutically acceptable carrier suitable for transdermal delivery" includes a carrier
capable of delivering the amine containing compound transdermally as defined above.
Suitable carriers for transdermal delivery of pharmaceuticals are described in U.S.
45 Patent No. 5,446,070, the contents of which are incorporated herein by reference.
Briefly, pharmaceutically acceptable carriers of the present invention include any
35 suitable finite (*i. e.*, solid) or non-finite (*i. e.*, non-solid, such as liquid or semi-liquid)
carrier including liquids, semi-liquids or solid carriers, such as a bioadhesive. Thus, the
50 amine containing compounds having biphasic solubility may be admixed with a

pharmaceutically acceptable carrier such as a cream, gel, emulsion, lotion, salve, paste, plaster, ointment, spray solution, or any other "non-finite" carrier known in the art of pharmaceutical delivery. For example, the base of a non-finite carrier may be lipid including phospholipids such as lecithins; fatty oils; lanolin; vasoline; paraffins; glycols; higher fatty acids; and higher alcohols.

The term "bioadhesive" as used herein includes an adhesive which attaches to a biological surface such as skin or mucosal tissue. Preferably, the bioadhesive of the present invention is self-adhesive in that it attaches to the site of interest without the need to reinforce its attachment by way of another adhesive. Suitable bioadhesive include natural or synthetic polysaccharides such as cellulose derivatives including methylcellulose, cellulose acetate, carboxymethylcellulose, hydroxyethylcellulose and the like; pectin; a mixture of sulfated sucrose and aluminum hydroxide; hydrophilic polysaccharide gums including natural plant exudates, such as karaya gum, ghatti gum, tragacanth gum, xanthan gum, jaraya gum and the like; seed gums including guar gum, locust bean gum, psillium seed gum and the like; and lecithins such as soya lecithin. In addition to the above ingredients, compositions of the present invention may also include other ingredients such as various pharmaceutically acceptable additives available to those skilled in the art. These additives include binders, stabilizers, preservatives, flavorings, fragrances, and pigments.

In another embodiment, the pharmaceutically acceptable carrier of the present invention includes van pen cream (cetyl alcohol, stearyl alcohol, steric acid, glycerol monostearate, isopropyl myristate, soya lecithin, BHT alcohol 95%, simethicone, sodium hydroxide 30% solution, polyoxyl stearate, edetate disodium 5%, purified water, urea).

Other Pharmaceutical Compounds

In another aspect, the invention features a transdermal composition suitable for transdermal delivery, which includes a therapeutically effective amount of a pharmaceutical compound (e.g., a serotonin specific reuptake inhibitor, a mood stabilizing compound, a dopamine compound, a compound suitable for treating attention deficit hyperactivity disorder, a compound suitable for treating hypertension and akathisia, an analgesic compound, or a compound used in the treatment of impotence) and a pharmaceutically acceptable carrier suitable for transdermal delivery of the pharmaceutical compound.

As used herein, the term "pharmaceutical compound" includes compounds suitable for treating a targeted condition and capable of being delivered in active form, *in vivo*. Examples of pharmaceuticals include drugs, enzymes, chemical compounds, combinations of chemical compounds, biological macromolecules and analogs thereof. Examples of pharmaceutical compounds are described in detail below.

5 In one embodiment of the invention, the pharmaceutical compound is a serotonin
specific reuptake inhibitor (SSRI). SSRIs are commonly prescribed for patients with
diagnoses of mood disorders, some forms of anxiety disorder (particularly panic
disorder), obsessive compulsive disorders, some forms of menopausal disorders, and
10 5 eating disorders (especially bulimia nervosa). Examples of such SSRIs include
sertraline (sold under the trade name Zoloft), paroxetine (sold under the trade name
Paxil), fluoxetine (sold under the trade name Prozac), venlafaxine (sold under the trade
name Effexor), and fluvoxamine (sold under the trade name Luvox).

15 In another embodiment of the invention, the pharmaceutical compound is a
10 mood stabilizing medication, such as carbamazepine (sold under the trade name
Tegretol) and valproic acid (sold under the trade name Depakote). These agents are used
frequently in psychiatric practice as either augmentation medications (to render
antidepressants more effective) or as anti-manic medications in the treatment of bipolar
20 mood disorder. Mood stabilizing medications are also used in neurologic practice for the
15 treatment of seizure disorders and for the treatment of certain pain disorders.

25 In yet another embodiment of the invention, the pharmaceutical compound is a
compound used for treating Attention Deficit Hyperactivity Disorder (ADHD), one
example of which is permoline, sold under the trade name Cylert. Permoline is a
medication that is used in the treatment of Attention Deficit Hyperactivity Disorder in
20 children and adults. It is practically insoluble in water, but soluble in ethylene glycol and
lipids, making it a good candidate for transdermal administration.

30 In a further embodiment of the invention, the pharmaceutical compound is a
dopamine compound, used for treating Parkinson's disease, examples of which are
pergolide, sold under the trade name Permax and bromocriptine mesylate, sold under the
25 trade name Parlodel.

35 In yet another embodiment of the invention, the pharmaceutical compound is a
compound used for treating hypertension and akathisia, one example of which is
propranolol, sold under the trade name Inderal.

40 In yet a further embodiment of the invention, the pharmaceutical compound is a
30 compound used in the treatment of impotence such as sildenafil, sold under the
tradename Viagra. It is believed that transdermal administration of sildenafil may be
useful, for at least some subjects, as compared to oral administration which has been
found, in at least some situations, to be associated with gastrointestinal side effects.

45 35 Methods For Preparing The Transdermal compositions

Another embodiment of the present invention provides a method for preparing
the above described transdermal compositions, by admixing a therapeutically effective
50 amount of the amine containing compound having biphasic solubility, optimally an

5 agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant, optimally an anti-inflammatory compound with the carrier suitable for transdermal delivery of the amine containing compound.

10 In one embodiment of the present invention, a transdermal composition is prepared by dispersing or dissolving crushed tablets, capsules or other preparation(s) of the amine containing compound having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds, which were intended for oral delivery, in a gel formed of soya lecithin and isopropyl palmitate or isopropyl myristate, alcohol, or ethoxy diglycol. In another embodiment of the present invention, Pluronic gel, formed of Pluronic such as Pluronic F127, potassium sorbate and water is used.

15 In a particular embodiment of the present invention, a transdermal composition including a combination of doxepin with guaifenesin is useful for treating pain. It is believed that transdermal administration of such combination can be advantageous, for at least some patients, as compared to oral administration, because higher local pharmaceutical concentrations at the site(s), e.g., of injury, can be achieved yielding an improved therapeutic response without systemic side effects such as weight gain, drowsiness, gastrointestinal upset and/or other known side effects of these pharmaceuticals.

20 Methods For Use

30 In one embodiment, the invention feature methods for treating pain in a subject in which the subject is contacted with a transdermal composition including an amine containing compound having biphasic solubility in an amount effective to treat pain in the subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound to thereby treat pain in the subject. In a preferred embodiment, the transdermal composition is applied to the skin of the subject as often as needed for the alleviation of pain. For example, the transdermal composition may be applied daily, weekly, monthly, yearly, for a length of time sufficient to alleviate pain.

35 Detailed examples of the preparation are provided below, along with examples of results obtained from transdermal administration to human patients. Preferably, a gel preparation is applied to the skin at the site or sites of pain. Patients can be evaluated by means of a structured evaluation form, e.g., completed at a frequency of at least one time per week. Evaluation of patients are for the present symptoms as well as any side effects from currently administered medications. This makes it possible to note changes on an ongoing basis.

40 Compositions of the invention can be self-administered doses in the form of a gel applied to the skin by the patient, or be implemented by providing a transdermal preparation in premeasured doses preferably in connection with an adhesive or other

5 covering or patch so that the dosage may be administered e.g., by placing the adhesive
patch on the skin of the patient. Although some embodiments of the invention have been
described in connection with positioning the pharmaceutical gel on the arm of a patient,
other positioning on the skin of a patient can also be used. Because, depending on the
10 formulation, speed or duration of transdermal delivery may vary as function of skin
location, in one embodiment the location of the skin to which the pharmaceutical is
applied is selected so as to relatively increase or decrease the delay, speed, duration, or
rate of delivery of the pharmaceutical, either with respect to a particular tissue or
systemically.

15 For example, when a rapid rise in blood serum levels is desired, a placement
which enhances delivery rate, such as behind the ear, can be used. When it is desired to
enhance dose or delivery rate locally, the transdermal formulation may be positioned
adjacent the desired treatment area. Membranes or matrices, such as a polymer matrix,
20 may be used to limit or control delivery rates. In addition to transdermal gel or patch
delivery, delivery of the transdermal or aerosol formulation can be achieved, e.g. by
administration as nose drops, eardrops, eyedrops and/or suppositories.

25 In one embodiment, medications dispensed in transdermal gel form will be
dispensed in unit doses, such as blister packs. The gel will be extruded from the blister
pack, and rubbed on the administration site. The dosage will be adjusted by varying the
20 number of unit dose applied. This will ensure accurate dosimetry and will avoid
contamination of the gel.

Methods For Selecting A Compound Suitable For Treating Pain

30 In a further aspect, the invention features a method for selecting a compound
suitable for treating pain in a subject. The method includes transdermally administering
35 an amine containing compound having biphasic solubility to a subject; and determining
whether pain is treated in the subject to thereby select a compound suitable for treating
pain in a subject. In a preferred embodiment, the method can further include modeling
the compound using a computer equipped with a three-dimensional chemical structure
40 modeling program (e.g., Molecules-3D Professional Edition, version 2.60, copyright
1991-1998, Molecular Arts Corp., © 1994-1998 WCB/McGraw Hill); and determining
whether the three-dimensional chemical structure of the compound possesses sufficient
characteristics to be useful as a sodium channel blocker, thereby selecting a compound
45 suitable for treating pain in a subject.

50 The effectiveness of the amine containing compound having biphasic solubility
to treat pain can be tested *in vitro* or *in vivo*. An animal model for pain, e.g., such as the
one described in Kral M.G. *et al.* (1999) *Pain* 81(1-2):15-24 can, for example, be used
for testing such compounds.

5 This invention is further illustrated by the following examples which should not
be construed as limiting. The contents of all references, patents and published patent
10 applications cited throughout this application, as well as the Figures are incorporated
5 herein by reference.

EXAMPLES

Example 1

15 One hundred grams of lecithin soya (granular) and 0.66 grams sorbic acid (NF-
FCC powder) were dispersed in 100 grams (117 milliliters (mL)) of isopropyl palmitate
20 NF and allowed to stand overnight. Approximately 220 milliliters of lecithin-isopropyl
palmitate in a form of a liquid of a syrup consistency was formed.

Example 2

25 One hundred grams of lecithin soya (granular) and 0.66 grams sorbic acid (NF-
FCC powder) is dispersed in 100 grams (117 milliliters) of isopropyl myristate NF and
allowed to stand overnight. Approximately 220 milliliters of lecithin-isopropyl myristate
30 in a form of a liquid of a syrup consistency was formed.

Example 3

35 A beaker was prepared by measuring to a volume of 100 milliliters. It was
considered important to measure the volume accurately rather than using beaker
25 markings. An amount of Pluronic F127 NF (20 grams for a 20 percent gel, 30 grams for
a 30 percent gel, 40 grams for a 40 percent gel) was mixed with 0.3 grams potassium
40 sorbate NF. Refrigerated purified water was added in an amount sufficient to bring the
volume to 100 milliliters. When all of the granules had been wet the gel was
refrigerated. Solution took place upon cooling, taking 12 to 24 hours. The resulting 100
30 milliliters of Pluronic gel was kept refrigerated, since the gel will solidify at room
45 temperature.

Example 4

Nine grams of carbamazepine in tablet form was ground in mortar and pestle. 4.3 milliliters of ethoxy diglycol was added and mixed to form a creamy paste. 13.2 milliliters of soya lecithin was added and mixed until smooth. The resulting 24 cc of solution was put into a 60 cc syringe. About 36 cc Pluronic F127 gel 20 percent (made according to Example 3) was placed in another syringe. The material was mixed well between syringes to yield 60 cc of carbamazepine organogel having a strength of 150 milligrams (mg) per milliliter. In some cases, the mixture was run through an ointment mill to reduce particle size.

Example 5

Sixty 100 milligram tablets of bupropion were ground and strained to form a fine powder. The bupropion powder was dissolved in 30 cc purified water, placed in a filter and washed with 10 to 20 cc purified water. The filtrate was used to make a 20 percent Pluronic gel using the procedures from Example 3, substituting filtrate for an equivalent volume of water, and stored in a refrigerator. Thirteen milliliters of soya lecithin was mixed with one-half the bupropion Pluronic gel and mixed between syringes to form a first batch. Thirteen milliliters of soya lecithin was mixed with the second half of the bupropion Pluronic gel and mixed between syringes to form a second batch. To each batch was added sufficient Pluronic gel F127 (made according to example 3) to yield a total of two 60 cc batches of bupropion HCl organogel having a strength of 15 milligrams per milliliter.

Example 6

600 milligrams of fluoxetine HCl (in the form of thirty 20 milligram capsules) was placed in a beaker and dissolved in approximately 18 cc of 95 percent ethyl alcohol. The solution was filtered through a filter funnel using fine filter paper. The residue was washed with 95 percent alcohol. The filtrate was heated, maintaining a temperature less than 85° C, to evaporate the alcohol to concentrate to 1 to 2 milliliters. 600 milligrams of isopropyl palmitate was combined with 600 milligrams of soya lecithin (granular), set aside and allowed to liquefy. Upon liquefaction, a thick syrupy consistency was obtained. 1.2 grams of the mixture was drawn into a 10 milliliter syringe and the alcoholic solution of fluoxetine HCl was drawn into another syringe. The two syringes

5 were attached together with a Luer-Luer adapter and the gel was thoroughly mixed. All
of the organogel was then transferred into one syringe and the empty syringe was
disconnected. Sufficient quantity of 20 percent Pluronic F127 gel (formed as described
in Example 3) was drawn into the empty syringe to make a total of 6 milliliters when
10 added to the volume in the other syringe. A Luer-Luer adapter was attached and the
contents of the two syringes was remixed until a smooth creamy mixture was obtained.
All the mixture was transferred into one syringe, the empty syringe was removed and the
Luer-Luer adapter was removed.

15 A Luer-oral adapter was attached to the mixture and transferred to six 1 milliliter
oral syringes, was filled with 1 milliliter of the gel. In this way, each syringe contained
10 five 20 milligram doses, or ten 10 milligram doses to yield a total of 60 doses of
fluoxetine in lecithin organogel having a strength of 10 milligrams per 0.1 milliliters.

Example 7

15 Twelve 250 milligram tablets of nefazadone were crushed in a mortar and pestle
25 and put through a strainer. 4.8 milliliters of ethoxy diglycol (8 percent) was added and
mixed. In cases in which all particles were not dissolved, 2 milliliters of Pluronic were
added and mixed. 13.6 milliliters of soya lecithin were added and mixed. The resulting
30 mixture was put into syringes with a Luer adapter and mixed well. Sufficient Pluronic
20 F127 gel, prepared according to Example 3, was added to achieve a volume of 60 cc and
mixed well to yield 60 cc of nefazadone organogel having a strength of 50 milligrams
per milliliter.

Example 8

25 Thirty 40 milligram tablets of paroxetine were crushed and run through a
strainer, discarding green coating material. 4.8 milliliters of ethoxy diglycol was added
40 to the powder and mixed in a mortar and pestle. Forty milliliters of Pluronic F127 gel 20
percent, formed according to Example 3, was added in graduated amounts to the powder
and mixed until smooth using a spatula. 13.2 milliliters of soya lecithin was added and
45 mixed well and the resulting material placed into syringes and sufficient quantity of
30 Pluronic gel was added to bring the volume to 60 milliliters. In those such cases where
particle size of the resulting material was too large, the cream was run through an

ointment mill to yield 60 milliliters of paroxetine organogel having a strength of 20 milligrams per milliliter.

Example 9

Thirty 100 milligram tablets of sertraline were crushed into a fine powder and strained, discarding the yellow coating. Sufficient amount of Pluronic F127 gel 20 percent (formed according to Example 3) was added to achieve a volume of 38 milliliters and mixed well in a mortar and pestle until a smooth cream was achieved. This material was placed into syringes and mixed between the syringes to obtain a compact cream. 13.2 milliliters of soya lecithin was added and mixed well between the syringes using about 20 pumps. Sufficient quantity of Pluronic F127 gel 20 percent was added to yield 60 milliliters of sertraline gel having a strength of 15 milligrams per milliliter.

Example 10

Venlafaxine hydrochloride has a solubility in water of 572 mg/mL (adjusted to ionic strength of 0.2 M with sodium chloride). Forty-five 100 milligram tablets of venlafaxine were crushed and put through a strainer. The powder was dissolved in 15 cc purified water, the solution placed into a filter and washed with 10 cc purified water. The filtrate was used to make a 20 percent Pluronic gel using the procedures of Example 3 (substituting the filtrate for an equivalent amount of water) and placed into a refrigerator overnight. 13.2 milliliters of soya lecithin were drawn into a syringe with a Luer loc. The venlafaxine Pluronic gel was drawn into another syringe coupled to the first syringe and mixed well. Sufficient Pluronic F127 gel was added to achieve a volume of 60 cc with a strength of 75 mg. per cc.

Example 11

15 grams of sodium valproate (Depakote) was ground in mortar and pestle. 4 mL of ethoxy diglycol was added and mixed well to form a creamy paste. 19.8 mL of soya lecithin was added and mixed until smooth. The resulting 24 cc of solution was put into 2 syringes with a Luer Loc and mixed well. The mixture was divided so that half is in each syringe. Using another 60 cc syringe, Pluronic 30% gel was added to each to bring each syringe to a volume of 45 mL.

5

Example 12

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Paroxetine hydrochloride has a solubility in water of 5.4 mg/mL. Paroxetine (Paxil) gel was prepared, according to the procedures of example 8. A dosage of 40 mg per day was self-administered by a 59 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 210 days, blood was drawn and blood serum level of Paxil was determined to be 0 nanograms (ng) per mL, while typical reference levels are 49 ± 26 ng/mL, indicating possible poor absorption or lab error. Clinical evaluation of the patient over a 210 day period of such transdermal administration indicated benefit to patient without GI side effects similar to that noted with oral preparation.

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10

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Example 13

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Sertraline hydrochloride is slightly soluble in water and isopropyl alcohol and sparingly soluble in ethanol. Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 100 mg per day was self-administered by a 54 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 19 days, blood was drawn and blood serum level of Zoloft was determined to be 5 ng/mL, while typical reference levels are 30-200 mg/mL indicating possible limited absorption or lab error.

30

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Example 14

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Fluoxetine hydrochloride has a solubility in water of 14 mg/mL. Fluoxetine (Prozac) gel was prepared, according to the procedures of example 6. A dosage of 20 mg per day was self-administered by a 54 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7 days, blood was drawn and blood serum level of fluoxetine was determined to be 45 ng/mL, while the plasma level of the primary active metabolite norfluoxetine was also 45 ng/mL. There was evidence of patient benefit from the clinical evaluation.

40

45

30

Example 15

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Carbamazepine is practically insoluble in water and soluble in alcohol and in acetone. Carbamazepine (Tegretol) gel was prepared, according to the procedures of

55

5 example 4. A dosage of 400 mg per day was self-administered by a 55 year old male
patient by application to the skin, for a period of at least 1 hour. No skin irritation was
reported. After 120 days, blood was drawn and blood serum level of Tegretol was
determined to be 4.6 micrograms (μg) per mL, while typical therapeutic levels are 4-10
10 11 μg /mL indicating good absorption. There were no GI side effects and the patient
demonstrated clinical improvement.

15 Example 16

Carbamazepine (Tegretol) gel was prepared, according to the procedures of
10 example 4. A dosage of 200 mg per day was self-administered by a 53 year old male
patient by application to the skin, for a period of at least 1 hour. No skin irritation was
reported. After 60 days, blood was drawn and blood serum level of Tegretol was
20 determined to be 10.8 μg /mL, while typical therapeutic levels are 4-10 11 μg /mL
indicating excellent absorption. There were no GI side effects and the patient
15 demonstrated clinical improvement.

25 Example 17

Sertraline (Zoloft) gel was prepared, according to the procedures of example 9.
30 A dosage of 50 mg per day was self-administered by a 53 year old male patient by
application to the skin, for a period of at least 1 hour. No skin irritation was reported.
20 After 63 days, blood was drawn and blood serum level of Zoloft was determined to be
23 ng/mL, while typical reference levels are 30-200 mg/mL. The patient demonstrated a
35 good clinical response without GI side effects.

25 Example 18

40 Carbamazepine (Tegretol) gel was prepared, according to the procedures of
example 4. A dosage of 200 mg per day was self-administered by a 47 year old male
patient by application to the skin, for a period of at least 1 hour. No skin irritation was
reported. After 91 days, blood was drawn and blood serum level of Tegretol was
45 determined to be less than 0.5 μg /mL, while typical therapeutic levels are 4-10 μg /mL,
30 indicating poor absorption, lab error, or patient non-compliance.

Example 19

Bupropion is highly soluble in water. Bupropion (Wellbutrin) gel was prepared, according to the procedures of example 5. A dosage of 100 mg per day was selfadministered by a 47 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 44 days, blood was drawn and blood serum level of Wellbutrin was determined to be less than 0.5 ng/mL, while typical therapeutic levels are 10-30 indicating poor absorption, lab error, or patient non-compliance.

Example 20

Fluoxetine gel was prepared, according to the procedures of example 6.. Typically, a total daily adult dosage of fluoxetine as applied to the skin according to the present invention is between about 20mg and 200 mg, more preferably between about 120 mg and about 200 mg. Dosages for non-adults and/or non-human mammals may need to be adjusted, e.g. proportionally to body weight. A dosage of 20-60 mg per day was self-administered by 5 patients, including that of example 13 and also including a 44 year old male patient, a 53 year old female patient, a 47 year old male patient and a 36 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 30-180 day period of such transdermal administration indicated a clinical response ranging from complete remission of symptoms to moderate improvement.

Example 21

Fluoxetine gel was prepared, according to the procedures of example 6. A dosage of 80-160 mg per day was self administered by a 50 year old female by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7 days at the 80 mg dosage level blood was drawn and the blood serum of fluoxetine was determined to be 34 ng/mL fluoxetine and 25 ng/mL norfluoxetine, while typical reference levels are 50-480 ng/mL, indicating good absorption. There was evidence of patient benefit from the clinical evaluation. The dosage was then increased to 160 mg per day and administered by the same method. After 7 days at the 160 mg dosage level blood was drawn and the blood serum level of fluoxetine was determined

to be 90 ng/mL fluoxetine and 25 ng/mL norfluoxetine, indicating good absorption. There was evidence of increased patient benefit at this higher dosage level which correlated positively with the higher plasma level. The patient has been receiving the medication continuously for a period of 5 months.

Example 22

Fluoxetine gel was prepared, according to the procedures of example 6. A dosage of 80-160 mg/day was self administered by a 38 year old female by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7 days at the 80 mg dosage level, blood was drawn and the blood serum level of fluoxetine was determined to be 25 ng/mL of fluoxetine and 25 ng/mL norfluoxetine. There was evidence of patient benefit from the clinical evaluation. The dosage was then increased to 160 mg per day and administered by the same method.

Example 23

Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 50-200 mg per day was self-administered by 6 patients, including those of examples 12 and 16 and also including a 60 year old male patient, a 53 year old male patient, a 48 year old male patient, a 38 year old male patient and a 47 year old male patient, by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 7-90 day period of such transdermal administration indicated responses ranging from complete resolution of depression to no noticeable response.

Example 24

Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 200-400 mg per day was self-administered by 6 patients, including those of examples 14, 15 and 17, and also including a 48 year old female patient, a 48 year old male patient and a 54 year old female patient, by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. The clinical evaluation of the patients over a 30-300 day period of such transdermal administration indicated responses ranging from moderate improvement to no positive clinical response.

Example 25

Paroxetine (Paxil) gel was prepared, according to the procedures of example 8. A dosage of 20 mg per day was self-administered by the patient of example 12 as well as by a 15 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. Clinical evaluation of the patients over a 30-210 day period of such transdermal administration indicated equivocal clinical improvement of the depression which may (or may not) have been related to the transdermally administered Paxil.

Example 26

Five 150 mg tablets of amitriptyline were crushed and run through a strainer. The powder was put into syringes with a Luer Loc and mixed well with 2 mL ethoxy diglycol. About 6 mL Pluronic Gel 20% was added and mixed well. 6.6 mL Soya Lecithin was added and mixed well. This mixture was thinned to 30-mL total volume with Pluronic Gel 20% and mixed well. The resulting mixture having a strength of 25 mg/mL was placed in appropriate dispensing device.

Example 27

Amitriptyline (Elavil) gel was prepared, according to the procedure of example 26. A dosage of 25 mg per day was self-administered by a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 100 day period of such transdermal administration indicated an apparently good clinical response, comparable to that achieved with oral medication.

Example 28

Trazodone (Desyrel) gel was prepared, according to a procedure similar to that of example 7. A dosage of 50-150 mg per day was self-administered by 2 patients, including a 36 year old female patient and a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a

42-90 day period of such transdermal administration indicated a good to excellent clinical response.

Example 29

5 Venlafaxine (Effexor) gel was prepared, according to a procedure similar to that of example 9. A dosage of 150-225 mg per day was self-administered by 2 patients, including a 54 year old female patient and a 55 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 15-165 day period of such transdermal administration indicated a response ranging from no clinical improvement to mild clinical improvement.

Example 30

Propranolol (Inderal) gel was prepared, according to a procedure similar to that of example 8 to produce a gel having a strength of 40 mg of propranolol per mL of gel. A dosage of 80 mg per day was self-administered by 2 patients, including a 36 year old female patient and a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 100 day period of such transdermal administration indicated results comparable to those achieved with oral medication.

Example 31

Bupropion (Wellbutrin) gel was prepared, according to a procedure described in example 5. A dosage of 150-200 mg per day was self-administered by 3 patients, including that of example 18, and also including a 38 year old male patient and a 53 year old female patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 5-45 day period of such transdermal administration indicated equivocal results.

Example 32

Valproic acid (Depakote) gel was prepared, according to a procedure similar to that of example 4. A dosage of 1000 mg per day was self-administered by a 38 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 30 day period of such transdermal administration indicated results comparable to those achieved with oral medication.

Example 33

Valproic acid (Depakote) gel was prepared according to the procedure of example 11. A dosage of 500-1000 mg was self administered by two male patients, ages 41 and 49. Administration was by application to the skin, for a period of at least one hour. Significant skin irritation occurred with one patient, but no gastrointestinal side effects were reported. Clinical evaluation of the patients over a period of two months revealed improvement, but upon longer term follow-up it appeared that other factors may have been responsible. After 28 days, blood was drawn and a serum valproic acid level of 26 µg/mL was obtained for the 49 year old patient (while taking 250 mg twice daily), with a therapeutic reference range of 50-150 µg/mL. This indicated poor to fair absorption, and the dosage was raised to 500 mg twice daily, with a further improvement in clinical response. The 41 year old patient reported a good clinical response to an initial dosage of 250 mg administered twice daily, but a serum valproic acid level of only 1 µg/mL was obtained. The dosage was increased to 500 mg twice daily, and a similar serum valproic acid level was obtained. The disparity between the clinical response and the plasma level might be explained either by laboratory error or placebo effect.

Example 34

A gel containing reboxetine (sold under the trade name Edronax) is prepared according to a procedure similar to that described in example 5 but using reboxetine in place of bopropion. The resulting mixture will be self administered by patients by application to the skin for a period of at least 1 hour. No skin irritation or gastrointestinal side effects are expected. Clinical evaluation of patients over a 5-45 day period of such transdermal administration is expected to indicate a good response to treatment.

Example 35

Nefazodone (Serzone) gel was prepared, according to a procedure described in example 7. A dosage of 100 mg per day was self-administered by a 61 year old (male, female) patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 21 day period of such transdermal administration indicated a good response to treatment.

Example 36

1 gram of permoline tablets are crushed in a mortar and then dissolved in propylene glycol, just sufficient to effect dissolution. 3 mL of propylene glycol or 95% ethyl alcohol is added to form a paste. 6.6 mL soya lecithin is added to the mixture in the mortar. The mixture is placed in two syringes with a Luer Loc and mixed thoroughly. Each syringe is filled to 30 mL Pluronic F127 20% gel and mixed between syringes to produce a mixture having a strength of 33 mg/mL. The mixture is put in an appropriate dispensing device.

Example 37

A 16-year-old female with an established diagnosis of Attention Deficit Disorder had been treated successfully with oral pemoline (Cylert) for about 6 months. To potentially decrease the risk of liver damage associated with long-term use, permoline prepared according to the procedure of example 36 will be administered transdermally, by application to the skin in the post auricular region for a period of at least one hour, at two sites, twice daily. No skin irritation is expected. The clinical results are expected to be comparable to those obtained with the oral medication, although the dosage may have to be adjusted upwards to achieve adequate plasma levels, and more time may be required to achieve satisfactory plasma levels.

For psychiatric patients, some have received two or more psychopharmaceuticals, and in some cases, two or more of the above examples describe different evaluations for the same period of administration of a psychopharmaceutical agent.

5 Of the patients who have received prescriptions for one or more of the
medications as described in the examples above, each had previously demonstrated a
significant intolerance to oral administration of one or more medications, prior to
instituting transdermal administration. The laboratory measures of plasma blood levels
10 5 described above for transdermally administered fluoxetine and carbamazepine are
believed to demonstrate good absorption transdermally using lecithin organogel matrix
as the vehicle. Valproic acid and sertraline do not appear to be absorbed well or reliably.
Valproic acid appears to cause skin irritation in some patients necessitating
15 discontinuation. Both the laboratory measure of Bupropion and the patient clinical
10 responses indicated poor or equivocal absorptions and results. Patient tolerance of
transdermal administration has been good to excellent. Patients in the example above
who suffered very severe GI side effects using oral preparations were more tolerant of
20 the inconvenience of rubbing on the gel than were patients who had experienced only
mild to moderate side effects. In general, more highly motivated and
15 treatment-compliant patients also had a higher rate of sustained compliance.

25 Patients in the examples above were evaluated by means of a structured
evaluation form depicted in Fig. 1, which was completed at a frequency of at least one
time per week for each patient receiving transdermal medication according to the
present invention. The patients were evaluated both for all present psychiatric symptoms
30 20 as well as any side effects from currently-administered medications. In general, it is
believed that patients with the most clear cut and uncomplicated diagnosis of major
depression experienced the best results. In general, patients with severe personality
35 disorders or with concealed substance abuse disorders did less well.

25 Example 38

40 1800 mg of gabapentin in powder form is dissolved with 1 mL propylene glycol
in syringes with a Luer Loc. 6.6 mL of Soya lecithin is added and mixed thoroughly
between syringes. The resulting material is placed in a device for dispensing measured
amounts.

45 30 Example 39

50 Gabapentin mixtures of 2% and 4% will be prepared by substituting 1200 mg
gabapentin or 600 mg gabapentin in place of 1800 mg gabapentin, in example 38.

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Example 40

Gabapentin, prepared according to Example 38 or 39, will be combined with either 3% or 5% Lidocaine in varying ratios.

Example 41

4% gabapentin, prepared according to Example 38 or 39, will be combined with 7% carbamazepine and 7% amitriptyline.

Example 42

2% gabapentin, prepared according to Example 38 or 39, will be combined with 2% carbamazepine and 1 % Piroxicam, which is expected to yield better penetration into muscle tissue.

Example 43

Gabapentin, prepared according to Example 38 or 39, in concentrations ranging from 2%-6% will be combined with clonidine in concentrations between .2% and .3%.

Example 44

A 56-year-old woman had painful upper and lower extremity spasms as a result of spastic quadriparesis resulting from an injury. Oral gabapentin, an anticonvulsant, had been administered previously, but had caused a "drugged" feeling, one of the commonly reported side effects with this agent. It was believed that use of transdermal gabapentin might provide local relief by achieving high local tissue concentrations near the site of administration without correspondingly elevated blood plasma levels. It is known that other anticonvulsants, such as carbamazepine, are useful in reducing neurogenic pain. Gabapentin's solubility in water exceeds 10%, making systemic absorption less likely. Gabapentin prepared according to the procedure of example 38 was self-administered by application to the skin in the area of pain. The patient reported moderate relief of spasms over a period of one week, with no systemic side effects and no report of skin irritation.

Example 45

Six grams of amitriptyline powder was placed in 40 milliliters of Pluronic F127 33% gel and placed under refrigeration to dissolve. Two milliliters of ethoxy diglycol was added to 4.8 grams of carbamazepine and mixed to form a smooth paste. 16.4 grams of soya lecithin was added to the resulting paste and mixed well. The dissolved amitriptyline composition was added to the carbamazepine composition and sufficient Pluronic F127 20% was added to make 120 milliliters and the resulting composition was mixed well to yield a composition having 5% amitriptyline and 4% carbamazepine.

Example 46

6 grams of doxepin was added to 20 milliliters Pluronic 33% F127 and put into a refrigerator to dissolve. 24 grams of ketoprofen and 12 grams of guaifenesin was added to 10 milliliters of 95% alcohol and mixed well. 26.4 milliliters of soya lecithin was added and mixed well and the doxepin composition was mixed with the ketoprofen/ guaifenesin composition. The resulting mixture was added to sufficient Pluronic 33% to yield 120 milliliters. The resulting composition was mixed well to yield a composition having about 20% ketoprofen, 5% doxepin and 10% guaifenesin.

Example 47

6 grams of doxepin was added to 26 milliliters Pluronic 33% and refrigerated to dissolve. 2 milliliters ethoxy diglycol was added 4.8 grams carbamazepine and mixed. The resultant mixture was added to 24 grams ketoprofen and six milliliters alcohol and the result was mixed well. 26.4 milliliters soya lecithin was added to the ketoprofen composition and mixed well. The doxepin composition was mixed with the carbamazepine/ ketoprofen composition and sufficient Pluronic 33% was added to yield 120 milliliters. The resultant composition was mixed well to yield a composition having about 20% ketoprofen, 4% carbamazepine and 5% doxepin.

Example 48

.15 grams sildenafil was crushed and strained and dissolved in 5 milliliters Pluronic 20% F127 and mixed between syringes. 2.2 milliliters of soya lecithin was added and mixed. Sufficient Pluronic 20% was added to yield 10 milliliters and the

5 resultant composition was mixed well to yield a composition having the strength of
about 15 milligrams per milliliter.

Example 49

10 5 A mixture of Sildenafil 15 mg/ml was applied to the penis and scrotum of a 51
year old male. An immediate and strong erection resulted with sexual stimulation,
without any irritation or burning. It is believed the composition will possess the
15 therapeutic results claimed for orally administered Sildenafil, without any time delay,
without any systemic GI side effects, and possibly without the degree of drug interaction
10 with nitrates used in cardiac disease. It is believed that this will contribute both to the
convenience of use of the pharmaceutical and to its safety.

Example 50

20 Compositions according the examples 45 through 47, 53, 55 were transdermally
15 applied to numerous patients, for the purpose of treating pain including as described in
25 other examples herein, with the results summarized in Table I below. The meaning of
certain entries in Table I is indicated in Table II below. Blank results indicate no
treatment at the pertinent site for this patient. Where a given line of Table I shows more
30 than one site, one "best" (greatest pain relief) result is shown in bold.

TABLE I

Patient	Age	Gender	Surgery	Pain	Medication							Duration	Result (Best result in Bold)									
					Ketoprofen	Gabapentin	Piroxicam	doxepin	carbamazepine	amitriptyline	gabapentin		shoulder	back	neck	elbow	knee	wrist	arm	ankle	hip	leg
A	50	2	2	3	10	3	4					2		0								
B	61	1	1	3				5				4				2.0						
B	61	1	1	3					4			12	2.0	2.0	2.0	2.0						
B	61	1	1	3	10	4	3					6							3.0			
C	41	2	1	2					4	5		2		1.0								
D	53	1	2	1	10	4	1					1			.8							
E	57	2	2	3	10	4		5			1	1		2.0			1.5					1.0
E	57	2	2	3	10	4	3					2	1.0	2.0				1.0				
F	38	2	2	3				10	5		5	2	2.0			3.0						
F	38	2	2	3		4			4			8	2.0						1.5			
F	38	2	2	3	10	4	1		4			4	2.0						1.0			
G	39	1	1	2	20	4		5	4			6					3.0					
H	61	1	1	3	10	4	3					4		2.0								

TABLE I (cont.)

Patient	Age	Gender	Surgery	Pain	Medication							Duration	Result (Best result in Bold)																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																		
					Wt% in lecithin organogel								Leg	Hip	Ankle	Arm	Wrist	Knee	elbow	neck	back	shoulder																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																									
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TABLE I (cont.)

Patient	Age	Gender	Surgery	Pain	Medication							Duration	Result (Best result in Bold)										
					Wt% in lecithin organogel								Leg	Hip	Ankle	Arm	Wrist	Knee	elbow	neck	back	shoulder	
K	40	1	2	3				5				6	4.0										
								6															
K	40	1	2	3			3	6				4	1.0						0				
L	35	2	2	2			3					8	1.0										
L	35	2	2	2				3				6		3.0					0		1.5	2.0	
M	38	1	2	1				4	3			2	1.5					0					
N	47	2	1	2						3		3	3.0	3.0	4.0		1.0						
N	47	2	1	2			1					2.0	0		2.0			2.0					

TABLE I (cont.)

Patient	Age	Gender	Surgery	Pain	Medication							Duration	Result (Best result in Bold)									
					ketoprofen	gabapentin	piroxicam	doxycipin	carbamazepine	amitriptyline	gabapentin		shoulder	back	neck	elbow	knee	wrist	arm	ankle	hip	leg
O	37	2	1	2	20	4		3				24	2.0		3.0							
O	37	2	2	2	10	4	3					24	1.0	.0								
P	31	2	2	2	13	3		3				2		4.0								
Q	31	2	1	2	20			3			10	1		2.0			1.5					
R	33	1	1	2					4	3		0					.0					
R	35	1	1	2	10	4	1					1		1.0								
S	33	1	1	2	10	4	1					16										
T	30	2	2	1	10	4	1					16					2.0	1.0		2.0		
U	43	1	2	2	10	4	3					2		.0								
V	37	2	1	3					6			8					3.0					
V	37	2	1	3	10	4	1					3					1.0					
W	33	1	2	1	10	4	1					8		1.0								
X	46	1	1	3	10			3	4			8		2.0	2.0	2.0						
Y	48	1	1	3				5				4	2.0	2.0								
Y	48	2	1	3	10	4	1					4				1.5		1.3			.0	

TABLE I (cont.)

Patient	Age	Gender	Surgery	Pain	Medication Wt% in lecithin organogel							Duration	Result (Best result in Bold)											
					Ketoprofen	Gabapentinum	Piroxicam	doxepin	carbamazepine	Amitriptyline	gabapentin		shoulder	back	neck	elbow	knee	wrist	arm	ankle	hip	leg		
AA	53	2	2	1		10	4	1					4		1.0									
BB	58	2	1	3		20	4			4	Hand	1	8		2.0								2.0	
CC	59	1	1	2					5				2		2.0	2.0					2.0			
CC	59	1	1	2		10	4	1					20		1.0	2.0			2.0					
CC	59	1	1	2		10	4	3					1						3.0			3.0		
DD	58	1	1	2		10	4	3					12			1.0			2.0					
EE	45	2	2	2		10	4	3					24	1.5		1.0								
FF	44	2	1	3		10	4	3					20	2.0										
GG	35	1	1	3		20	4						4				1.0		1.0					

Patient	Age	Gender	Surgery	Pain	Medication							Duration	Result (Best result in Bold)																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																									
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Patient	Age	Gender	Surgery	Pain	Medication Wt% in lecithin organogel							Duration	Result (Best result in Bold)											
					Ketoprofen	Gabapentinm	Piroxicam	doxepin	carbamazepin	amitriptylinec	guifenesin		shoulder	back	neck	elbow	Knee	Wrist	Arm	Ankle	Hip	Leg		
MM	42	2	1	3						4			8		.0	4.0				2.0				1.0
MM	42	2	1	3		10		3		4			12		.0									
MM	42	2	1	3					5				4							2.0				1.0
NN	41	1	2	2		10	4	3					2		.0									

TABLE II

Gender: 1 = male

2 = female

Surgery: 1 = one or more surgeries

2 = no surgeries

Pain: 1 = mild

2 = moderate

3 = severe-sufficient to
produce observed tears

Duration: length of treatment trial in weeks

Result: 0 = no benefit

1 = mild benefit

2 = moderate benefit (greater than 25% pain reduction)

3 = major benefit (greater than 40-45% pain reduction)

4 = almost complete relief (greater than 80% pain reduction)

Certain results drawn from the information of Table I are summarized in Table III and IV.

Table III - Percent reported pain relief

Site	N (Number of data points)	None	Mild	Mild- moderate	moderate	Major	Total
Wrist	13	16.7	33.3	8.3	41.7		
Shoulder	14	7.1	21.4	14.3	42.9	7.1	7.1
Elbow	5		40	20	20	20	
Back	25	24	32	8	28	8	
Arm	7	28.6	14.3	14.3	28.6	14.3	
Neck	11	9.1	18.2		45.5	9.1	18.2
Knee	13	15.4	46.2	15.4	7.7	15.4	

Table IV (percent reported pain relief)

	N	None	Mild	Mild-moderate	moderate	Major	Total
Best result without tricyclic	36	16.7	36.1	8.3	27.8	8.3	2.8
Best result with any tricyclic	20	10	10	20	35	15	10
Either tricyclic -sole agent	7		14.3	14.3	42.9	14.3	14.3
Best result with ketoprofen gabapentin piroxicam	25	16	44	4	28	8	
Best result without doxepin	43	18.6	32.6	14	23.3	7	4.7
Best result with doxepin	13		7.7	7.7	53.8	23.1	7.7

Example 51

A 51 year old female administered a composition prepared according to example 46, containing 20% ketoprofen, 5% doxepin, and 10% guaifenesin to her back for a period of 2 weeks. She reported moderate pain relief, lasting several hours, after each application. She reported no skin irritation nor any other side effects. Oral medications had produced no relief, and had caused significant GI side effects.

Example 52

A 34 year old man administered a composition containing 20% ketoprofen, 4% carbamazepine, and 5% doxepin to a very severely scarred wrist that had undergone 4 surgeries for carpal tunnel syndrome. He reported moderate pain relief, lasting for several hours after each application. No other treatment, including opiate oral pain medication, had been effective in providing even minor pain relief.

Example 53

24 grams ketoprofen and sufficient guaifenesin to result in a 10% final guaifenesin concentration, was mixed well with 10 milliliters 95% alcohol. 1200 mg gabapentin was dissolved in one ml propylene glycol in a syringe with a luer loc. 26.4 ml of soya lecithin was added to the ketoprofen-guaifenesin-alcohol mixture and mixed well. The resulting mixture was added to the gabapentin-propylene glycol mixture and mixed well. 4.8 gm of carbamazepine was combined with the resultant combination and mixed well to form a smooth paste. The resulting paste was combined with the ketoprofen-guaifenesin-alcoholgabapentin mixture and mixed well with sufficient

5 pluronic to yield 120 ml of a composition containing ketoprofen 20%, carbamazepine
4%, gabapentin 4%, guaifenesin 10%.

10 Example 54

5 A 58 year old female with damage to her cervical spinal cord with a resultant
spastic quadreparesis reported moderate relief of both pain and muscle spasms when she
applied a mixture prepared generally according to example 53, containing ketoprofen
15 20%, carbamazepine 4%, gabapentin 4%, guaifenesin 10% for a period of 8 weeks to
her back and hip. She had been unable to tolerate both oral carbamazepine and oral
10 gabapentin because of systemic side effects, including skin rash with the carbamazepine
and dizziness and sedation with the gabapentin. She experienced no skin irritation nor
20 other side effects with the transdermal formulation.

Example 55

15 Six grams of doxepin powder combined with 26 milliliters pluronic and placed
25 in the refrigerator until dissolved. 1200 mg gabapentin was mixed with 1 ml propylene
glycol and placed in a syringe with luer lock. 6.6 ml of soya lecithin was added and
mixed well between syringes. 24 gm of ketoprofen and 8 milliliters alcohol was mixed
30 well between two syringes with luer loc. The doxepin mixture was mixed well with the
gabapentin mixture and subsequently the ketoprofen mixture was added and mixed well.
20 Sufficient pluronic 20% (about 54 ml) was added to yield 60 ml of a composition having
about 20% ketoprofen, 4% weight percent gabapentin and 5% weight percent doxepin.
35

Example 56

25 A 57 year old female applied a mixture, prepared generally according to example
40 55, containing ketoprofen 20%, gabapentin 4%, and doxepin 5% for a period of 8 weeks
to her neck and reported major relief. She applied the same mixture to her shoulder and
reported moderate relief. A mixture that substituted piroxicam for the doxepin produced
only mild shoulder relief.
45

30 Example 57

A 35 year old man with a history of knee injury with vascular compromise and 3
50 surgeries applied a mixture, prepared generally according to example 45, containing 4%

carbamazepine and 5% amitriptyline to his knee, and reported mild to moderate pain relief, without skin irritation nor other side effects.

Example 57A

A 41 year old woman with history of back surgery applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% gabapentin to her back for a period of 2 weeks. She reported mild pain relief.

Example 58

A 53 year old man with a history of two total bilateral knee replacements applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% amitriptyline to both knees for a period of 4 weeks. He reported no pain relief.

Example 58A

A 54 year old man with a history of 7 back surgeries applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% amitriptyline to his back for a period of 2 weeks. He reported mild to moderate pain relief, over and above that he was receiving from a transdermal opiate medication (Duragesic). He reported no side effects, and specifically no skin irritation.

Example 59

A 38 year old man with a history of shoulder strain applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% amitriptyline to his shoulder for a period of 2 weeks. He reported mild to moderate pain relief, and reported no skin irritation nor other side effects.

Example 61

Sufficient carbamazepine and gabapentin was added to a combination of soya lecithin and pluronic to yield a lecithin organogel having about 4% carbamazepine and 5% gabapentin.

Example 62

A 42 year old woman with a history of 3 back surgeries and cervical degenerative disc disease applied a mixture, prepared according to example 61, containing 4% carbamazepine and 5% gabapentin to her neck and reported total relief of pain. She reported no side effects, and no skin irritation. She noted the complete and rapid resolution of a migraine like headache at the same time. Administration of the same mixture to her arm and her wrist, affected by a diagnosed condition of reflex sympathetic dystrophy, yielded moderate pain relief.

Example 63

3.6 grams gabapentin was dissolved with 5.4 ml ethoxy diglycol using a mortar and pestle. 9.6 grams ketoprofen and 2.7 grams piroxicam were added and the resultant composition mixed well. 19.8 milliliters soya lecithin was added and resultant mixture mixed well and added to a sufficient quantity of 20% pluronic gel to yield 90 milliliters of a composition having about 10 percent ketoprofen, 4% gabapentin and 3% piroxicam.

Example 64

3.6 grams gabapentin was dissolved with 5.4 ml ethoxy diglycol using a mortar and pestle. 9 grams ketoprofen and 0.9 grams piroxicam were added and mixed well. 19.8 milliliters soya lecithin was added to the resultant mixture and mixed well. Sufficient amount of pluronic gel 20% was added to yield 90 milliliters of a composition having approximately 10% ketoprofen, 4% gabapentin and 1% piroxicam.

Example 65

12 g doxepin was mixed with 50 ml Pluronic F 127 33% and placed in a refrigerator to dissolve. 12 g gabapentin was dissolved in 9 ml ethoxy diglycol and mixed to form a smooth paste. 52.8 ml of soya lecithin was added and mixed well. The doxepin/Pluronic mixture was added and mixed well. Sufficient quantity of Pluronic F 127 20% was added to produce 240 ml of a composition having about 5 wt% gabapentin and 5 wt% doxepin.

Example 66

A 36 year old man with a knee injury involving joint surface damage and vascular compromise applied a mixture, prepared generally according to Example 65 to his knee several times per day. He reported moderate to major (40%) relief of pain that persisted for 4 to 6 hours. An earlier trial of carbamazepine-amitriptyline gel produced no relief when applied to his knee.

Example 67

6 gm doxepin was mixed with 18 ml of Pluronic 33% to and placed in a refrigerator to dissolve. 6 gm gabapentin was ground in a mortar and pestle to a fine powder, added to 6 ml ethoxy diglycol and mixed to form a smooth paste. 12 gm guaifenesin was added and mixed well. 26.4 ml soya lecithin was added and mixed well. The doxepin/Pluronic mixture was added and mixed well. Sufficient quantity of Pluronic gel (25.2 ml of 33% Pluronic, although 30% or 20% Pluronic can be used), was added to produce 120 ml of a composition having about 5 wt% gabapentin, about 5 wt% doxepin and about 10 wt% guaifenesin.

Example 68

A 55 year old woman with a back and shoulder injury sustained as a nursing care provider applied a mixture, prepared generally according to Example 67, to her back three times per day for a period of two weeks and achieved major relief. She applied the same mixture to her hip and leg and reported moderate to major relief. A mixture containing only doxepin provided only moderate relief to her back, and mild to moderate relief to her hip and leg. A mixture that contained only ketoprofen, gabapentin and piroxicam provided only mild relief to her back.

Example 69

A 59 year old woman with cervical and back strain applied a mixture, prepared generally according to example 51, but without steps involving ketoprofen) containing about 5 wt % doxepin and about 10 wt% guaifenesin, to her neck for a period of two weeks, two to four times per day, and achieved total relief. She applied the same mixture to her back and achieved major to total relief.

Example 70

4.5 gm of doxepin HCl was dissolved using 2.5 ml 95% alcohol and mixed well between syringes. It is also possible to mix the doxepin with 5 ml Pluronic 20% and place in a refrigerator to dissolve. Sufficient quantity of 20% Pluronic F127 was added to produce 90 ml of a composition having about 5 wt% doxepin. Preferably this and other disclosed compositions are protected from light.

Example 71

A 61 year old man with injuries to his back, neck and arm applied a mixture (prepared generally according to Example 70) to his neck four times per day and achieved major relief. He applied the same mixture to his elbow and achieved moderate relief.

Example 72

A formulation of 7% antidepressant and about 10% muscle relaxant was prepared by dissolving 3.15 g of trimipramine and 4.5 g of guaifenesin in a mixer jar using 2.7 mL of ethoxy diglycol. About 9.9 mL of soya lecithin was added and the mixture was mixed well. Sufficient quantity of Pluronic F127 NF (20%) to make total volume of about 45 mL was added and mixed well.

Example 73

A gel formulation of 30% NTHE was prepared from 36 g of celecoxib, 7.2 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (20%) to make total volume of 120 mL.

Example 74

A gel formulation containing about 7% antidepressant and about 13% muscle relaxant was prepared from 14.4 g of doxepin, 31.2 g of guaifenesin, 12 mL of ethoxy diglycol, 52.8 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 240 mL.

Example 75

A gel formulation containing 5% antiepileptic was prepared from 6 g of lamotrigine, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 76

A gel formulation containing 10% adrenergic agonist was prepared from 12 g of crushed tizanidine, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 77

A gel formulation containing 10% muscle relaxant was prepared from 12 g of crushed metaxalone, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 78

A gel formulation containing 10% muscle relaxant was prepared from 12 g of crushed carisoprodol, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 79

A gel formulation containing 10% methocarbamol was prepared from 12 g of crushed methocarbamol, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 80

A gel formulation containing 10% muscle relaxant was prepared from 12 g of crushed dantrolene sodium, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 81

A gel formulation containing 7% antidepressant, 10% muscle relaxant was prepared from 8.4 g of crushed doxepin, 12 g of chlorzoxazone, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 82

A series of experiments in human subjects were performed using various combinations of pharmaceuticals. The results are indicated in Figure 2.

Values of pain relief as rated by the patients are provided for each body part for which the medication was administered. The scale used in Figure 2, is as follows:

0	=	None	no benefit or equivocal benefit
1	=	Mild	less than 15% pain reduction

5	1.5	=	Mild-moderate	15-25% pain reduction
	2.0	=	Moderate	25-33% pain reduction
	2.5	=	Moderate-major	33-45% pain reduction
	3.0	=	Major	45-60% pain reduction
5	3.5	=	Major-total	60-80% pain reduction
	4.0	=	Total	greater than 80% pain reduction

10 For each body part and for each percentage composition of each compounded medication, the individual ratings as well as a mean, which is the statistical mean of the values given according to the scale listed above, are provided. For example, 3 patients were administered doxepin 5% to their back, and the mean level of relief was 2.333. By contrast, 13 patients received the 5%/10% doxepin-guaifenesin combination, and their mean level of pain relief was 2.885. Results for 7/10 and 10/10 compositions of doxepin guaifenesin are also given, and the mean for the entire sample of dox-guai in all combinations is provided at the end of the section, namely 2.722.

The abbreviations used in Figure 2 are as follows:

Abbreviations	Generic Pharmaceutical names
20 c-dox-gu	carbamazepine doxepin guaifenesin
c-gab-do	carbamazepine gabapentin doxepin
carb	carbamazepine
carb-ami	carbamazepine amitriptyline
carb-gab	carbamazepine gabapentin
25 dox	doxepin
dox-chl	doxepin chlorzoxazone
dox-guai	doxepin guaifenesin
g-dox-gu	gabapentin doxepin guaifenesin
gab-dox	gabapentin doxepin
30 k-ca-dox	ketoprofen carbamazepine doxepin
k-car-pi	ketoprofen carbamazepine piroxicam
k-dox-ch	ketoprofen doxepin chlorzoxazone
k-dox-gu	ketoprofen doxepin guaifenesin
k-dox-pi	ketoprofen doxepin piroxicam
35 k-g-do-g	ketoprofen gabapentin doxepin guaifenesin
k-gab	ketoprofen gabapentin
k-gab-ami	ketoprofen gabapentin amitriptyline
k-gab-do	ketoprofen gabapentin doxepin
k-gab-gu	ketoprofen gabapentin guaifenesin
40 k-gab-pi	ketoprofen gabapentin piroxicam
k-pi	ketoprofen piroxicam
la-li-gu	lamotrigine lidocaine guaifenesin
lam-chl	lamotrigine chlorzoxazone
n-dox-ch	naproxen doxepin chlorzoxazone
45 naproxen	naproxen
50 tri-chl	trimipramine chlorzoxazone

5 Based on the results described herein, doxepin appears to be an effective pain relief medication when administered transdermally and appears to be substantially free of side effects when administered transdermally as described herein.

10 Doxepin appears to provide about three times the positive response rate compared to at least some other pharmaceutical agents described herein, regardless of whether such other pharmaceutical agents are administered singly or in combination. Doxepin appears to be substantially more effective than amitriptyline as a pain, e.g., neuropathic pain agent when administered transdermally. This appears to be true regardless of whether doxepin is administered as a single agent or is administered in combination with other pharmaceuticals as described herein.

20 Carbamazepine appears to provide positive effects as a pain, e.g., neuropathic pain agent, at least in properly selected patients. Carbamazepine appears to cause a rash in at least some patients, requiring its discontinuation.

25 These side effects appear similar to those that are noted for oral administration of carbamazepine. Gabapentin appears to be free of side effects when administered transdermally. Although some patients appear to derive some benefit from a combination of transdermally administered ketoprofen, gabapentin, and piroxicam, the effect appears to be relatively weak compared to the effect provided by doxepin.

30 Guaifenesin appears to provide benefit as an adjunctive treatment, of painful spasticity. For the patient population described herein, amitriptyline appeared to offer limited pain relief when administered transdermally. It appears that combining gabapentin with doxepin may offer some additional benefit. The addition of guaifenesin to doxepin may be of particular value when painful spasticity is present.

35 In view of the above, the invention provides treatment to patients for whom oral delivery is suboptimal, such as patients who experience gastrointestinal or other side effects, patients who experience poor absorption for orally delivered pharmaceuticals and/or patients who benefit from delivery over an extended period or a relatively rapid delivery or higher rate of increase of plasma levels. The present invention achieves delivery of therapeutic amounts of pharmaceuticals, for at least some patient populations, substantially without skin irritation, gastrointestinal or other side effects associated with orally-delivered pharmaceuticals, especially psychopharmaceuticals, and yields clinical benefits comparable to or greater than those received by patients to whom corresponding pharmaceuticals were administered orally. In view of the above reasons,

particularly effective pain medications are those described in examples 65, 67, 69 and 70.

A number of variations and modifications of the invention can also be used. It is believed that blood plasma levels may be increased by providing for two or more transdermal applications per day and/or applying a transdermal composition to two or more sites.

In at least one case, application of a Prozac gel formulation twice daily appeared to approximately double the plasma level. It is believed that an approach such as applying a Prozac gel formulation twice daily to two sites will yield middle range therapeutic levels of about 140-250 ng/ml. At least partially on the basis of the results described herein for fluoxetine, it is believed olanzapine (sold under the trade name Zyprexa) or a fluoxetine/olanzapine mixture in a lecithin organogel will prove useful.

Other types of psychotropic or psychopharmaceutical medications for which the described transdermal delivery may be used including psychostimulant medications.

One example of a psychostimulant medication is Methylphenidate (sold under the trade name Ritalin) used in the treatment of attention deficit hyperactivity disorder (ADHD). Methylphenidate typically has a 2-4 hour duration of action necessitating frequent dosing of a patient which is particularly difficult to accomplish with children in school. It is believed that by using transdermal administration, it will be possible to achieve an extension of effective dosing throughout the day, eliminating the need for frequent oral medication administration. It is believed that transdermal administration will also eliminate peaks and valleys of blood plasma levels which, it is believed, will be more clinically effective. It is believed similar results will be obtained with other pharmaceuticals, for example, Dextroamphetamine (under the trade name Dexedrine) although it is believed the need is less acute since a time release "spansule" form of the medication is available which typically has a 5-6 hour duration of action. Another group of psychotropic medications which, it is believed, will benefit from transdermal delivery includes antipsychotic medication such as those used in the treatment in schizophrenia.

Embodiments of the invention include, but are not necessarily limited to, use by patients with enteric absorption deficits.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following

claims.

Claims

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WHAT IS CLAIMED IS:

1. A transdermal composition for treatment of pain in a subject comprising:
 - (a) an amine containing compound having biphasic solubility in an amount effective to treat pain in a subject; and
 - (b) a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound.
2. The transdermal composition of claim 1, further comprising an agent which enhances the activity of the amine containing compound having biphasic solubility.
3. The transdermal composition of claim 2, wherein the agent which enhances the activity of the amine containing compound having biphasic solubility is a muscle relaxant.
4. The transdermal composition of claim 1, wherein the amine containing compound is an antidepressant compound.
5. The transdermal composition of claim 4, wherein the antidepressant compound is a tricyclic antidepressant compound.
6. The transdermal composition of claim 1, wherein the amine containing compound is doxepin.
7. The transdermal composition of claim 1, wherein the amine containing compound is trimipramine.
8. The transdermal composition of claim 1, wherein the amine containing compound is a sodium channel blocker.
9. The transdermal composition of claim 1, wherein the pharmaceutically acceptable carrier is a lecithin organogel.
10. The transdermal composition of claim 3, wherein the muscle relaxant is selected from the group consisting of guaifenesin, chlorzoxazone, dantrolene sodium, metaxalone, carisoprodol, and combinations thereof.

5 11. The transdermal composition of claim 10, wherein the muscle relaxant is
guaifenesin.

10 12. The transdermal composition of claim 3, wherein the muscle relaxant is a
5 benzodiazepine.

15 13. The transdermal composition of claim 12, wherein the benzodiazepine is
clozapine.

20 14. The transdermal composition of claim 12, wherein the benzodiazepine
is diazepam.

25 15. The transdermal composition of claim 1, further comprising an
anti-inflammatory compound.

30 16. The transdermal composition of claim 15, wherein the anti-inflammatory
compound is a nonsteroidal anti-inflammatory compound.

35 17. The transdermal composition of claim 16, wherein the nonsteroidal
20 anti-inflammatory compound is selected from the group consisting of celecoxib,
etodolac, mefenamic acid, nabumetone, salsalate, naproxen, vioxx®, and combinations
30 thereof.

40 18. A transdermal composition for treatment of pain in a subject comprising:
25 (a) an amine containing compound having biphasic solubility in an
35 amount effective to treat pain in a subject;
 (b) a muscle relaxant in an amount effective to enhance the activity of
the amine containing compound having biphasic solubility; and
 (c) a pharmaceutically acceptable carrier suitable for transdermal
40 30 delivery of the amine containing compound and the muscle relaxant.

45 19. The transdermal composition of claim 18, wherein the muscle relaxant is
selected from the group consisting of guaifenesin, chlorzoxazone, dantrolene sodium,
metaxalone, carisoprodol, and combinations thereof.

50 20. The transdermal composition of claim 18, wherein the muscle relaxant is
guaifenesin.

5 21. The transdermal composition of claim 18, wherein the muscle relaxant has biphasic solubility.

10 22. The transdermal composition of claim 18, wherein the amine containing compound is an antidepressant compound.

15 23. The transdermal composition of claim 22, wherein the antidepressant compound is a tricyclic antidepressant compound.

20 24. The transdermal composition of claim 22, wherein the antidepressant compound is selected from the group consisting of doxepin, trimipramine, and combinations thereof.

25 25. The transdermal composition of claim 18, wherein the amine containing compound is doxepin.

30 26. The transdermal composition of claim 18, wherein the amine containing compound is a sodium channel blocker.

35 27. The transdermal composition of claim 18, wherein the pharmaceutically acceptable carrier is a lecithin organogel.

40 28. The transdermal composition of claim 18, further comprising an anti-inflammatory compound.

45 29. The transdermal composition of claim 28, wherein the anti-inflammatory compound is a nonsteroidal anti-inflammatory compound.

50 30. The transdermal composition of claim 29, wherein the nonsteroidal anti-inflammatory compound is selected from the group consisting of celecoxib, etodolac, mefenamic acid, nabumetone, salsalate, naproxen, vioxx[®], and combinations thereof.

55 31. A transdermal composition for treating pain in a subject comprising:
 (a) doxepin in an amount effective to treat pain in a subject;
 (b) guaifenesin in an amount effective to enhance the activity of doxepin; and

5 (c) a pharmaceutically acceptable carrier suitable for transdermal delivery of the doxepin and the guaifenesin.

10 32. The transdermal composition of claim 31, wherein the pharmaceutically acceptable carrier is a lecithin organogel.

15 33. The transdermal composition of claim 31, further comprising an anti-inflammatory compound.

20 34. A method of treating pain in a subject comprising contacting the subject with a transdermal composition comprising:

25 (a) an amine containing compound having biphasic solubility in an amount effective to treat pain in the subject; and

30 (b) a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound.

35 35. The method of claim 34, wherein the transdermal composition further comprises an agent which enhances the activity of the amine containing compound having biphasic solubility.

40 36. The method of claim 35, wherein the agent which enhances the activity of the amine containing compound having biphasic solubility is a muscle relaxant.

45 37. The method of claim 34, wherein the amine containing compound is an antidepressant compound.

50 38. The method of claim 37, wherein the antidepressant compound is a tricyclic antidepressant compound.

55 39. The method of claim 37, wherein the antidepressant compound is selected from the group consisting of doxepin, trimipramine, and combinations thereof.

40 40. The method of claim 37, wherein the antidepressant compound is doxepin.

45 41. The method of claim 34, wherein the amine containing compound is a sodium channel blocker.

5 42. The method of claim 34, wherein the pharmaceutically acceptable carrier is a lecithin organogel.

10 43. The method of claim 36, wherein the muscle relaxant is selected from the group consisting of guaifenesin, chlorzoxazone, dantrolene sodium, metaxalone, carisoprodol, and combinations thereof.

15 44. The method of claim 43, wherein the muscle relaxant is guaifenesin.

20 45. The method of claim 36, wherein the muscle relaxant is a benzodiazepine.

25 46. The method of claim 45, wherein the benzodiazepine is clozapine.

30 47. The method of claim 45, wherein the benzodiazepine is diazepam.

35 48. The method of claim 34, wherein the transdermal composition further comprises an anti-inflammatory compound.

40 49. The method of claim 48, wherein the anti-inflammatory compound is a nonsteroidal anti-inflammatory compound.

45 50. The method of claim 49, wherein the nonsteroidal anti-inflammatory compound is selected from the group consisting of celecoxib, etodolac, mefenamic acid, nabumetone, salsalate, naproxen, viox[®], and combinations thereof.

50 51. A method for selecting a compound suitable for treating pain in a subject comprising:

- 55 (a) transdermally administering an amine containing compound having biphasic solubility to a subject; and
 (b) detecting whether pain is treated in the subject to thereby select a compound suitable for treating pain in a subject.

60 52. A transdermal composition for treatment of pain in a subject comprising:
65 (a) a compound capable of blocking afferent neuron transmission in an amount effective to block afferent neuron transmission in a subject; and
 (b) a pharmaceutically acceptable carrier suitable for transdermal delivery of the compound.

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53. The transdermal composition of claim 52, further comprising an agent which enhances the activity of the compound suitable for blocking afferent neuron transmission.

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1/11

cpt 90862 Medication Management (cdw ver. 4-24-95)

90862.DOC

Patient: _____ Date _____

Current Medication: 1) _____
2) _____
3) _____
4) _____
5) _____
6) _____

Diagnoses: Axis 1: _____ Axis 3: _____
Axis 2: _____ GAF _____

Subjective: _____

Objective :	APPEARANCE _____	AFFECT _____
	SPEECH _____	CONCENTRATION _____
	MEMORY _____	IRRITABILITY _____
	APPETITE _____	AV HALLUC. _____
	CRYING SPELLS _____	ENERGY LEVEL _____
	SLEEP _____	WEIGHT _____

SIDE EFFECTS: _____

RESPONSE OF DEPRESSION SYMPTOMS TO MEDICATIONS:				
EXCELLENT	GOOD	FAIR	POOR	N/A

RESPONSE OF ANXIETY SYMPTOMS TO MEDICATIONS:				
EXCELLENT	GOOD	FAIR	POOR	N/A

CONCURRENT MEDICATION CONDITIONS: _____

ASSESSMENT: _____

PLAN: 1) Continue meds: _____
2) Change dosage: _____
3) New Med: _____
4) _____

LAB STUDIES ORDERED: _____
OTHER: _____

Fig. 1

Case Processing Summary(a)

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
ankle * MEDS * Composition	4	3.1%	127	96.9%	131	100.0%
arm * MEDS * Composition	10	7.6%	121	92.4%	131	100.0%
Back * MEDS * Composition	69	52.7%	62	47.3%	131	100.0%
elbow * MEDS * Composition	11	8.4%	120	91.6%	131	100.0%
headache * MEDS * Composition	131	100.0%	0	.0%	131	100.0%
Knee * MEDS * Composition	19	14.5%	112	85.5%	131	100.0%
hip * MEDS * Composition	15	11.5%	116	88.5%	131	100.0%
Neck * MEDS * Composition	28	21.4%	103	78.6%	131	100.0%
leg * MEDS * Composition	13	9.9%	118	90.1%	131	100.0%
shoulder * MEDS * Composition	25	19.1%	106	80.9%	131	100.0%
wrist * MEDS * Composition	26	19.8%	105	80.2%	131	100.0%
a Limited to first 150 cases						

P

					Case Number	ankle	arm
c-dox-gu	Composition	5/5/10	1		26	.	.
			2		33	.	.
			3		41	.	.
			4		59	.	.
			5		73	.	.
			6		80	.	.
		4/5/10	Total	N			
				Mean			
			1		98	.	.
			2		112	.	.
			Total	N			
				Mean			

Fig. 2

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		Total	N			
			Mean			
c-gab-do	Composition	5/5/5	1	34	.	.
			Total	N		
				Mean		
		Total	N			
			Mean			
		4	1	5	.	.
			Total	N		
				Mean		
carb	Composition	6	1	81	.	.
			Total	N		
				Mean		
		Total	N			
			Mean			
		4/5	1	12	.	.
			2	40	.	.
			3	49	.	.
			4	64	.	.
carb-ami	Composition		Total	N		
				Mean		
		Total	N			
			Mean			
		4/4	1	27	.	mild-moderate
			2	35	.	.
			3	126	.	moderate
carb-gab	Composition		Total	N		2
				Mean		1.750
		Total	N			2
			Mean			1.750
			1	4	.	moderate
			2	13	.	.
			3	15	.	.

Fig. 2 (cont'd)

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	dox	Composition	5	4	42	.	.
				5	46	.	none
				6	74	.	.
				7	95	moderate	.
				8	116	.	.
				9	121	.	.
				10	128	.	moderate
				Total	N	1	3
					Mean	2.000	1.333
			Total	N	1	3	
				Mean	2.000	1.333	
	dox-chl	Composition	7/13	1	10	.	.
				Total	N		
					Mean		
			5/10	1	21	.	.
				2	29	.	.
				3	30	.	.
				Total	N		
					Mean		
			7/10	1	83	.	.
				Total	N		
					Mean		
			Total	N			
				Mean			
				1	7	.	.
				2	9	.	.
				3	14	.	.
				4	18	.	.
				5	20	.	.
				6	25	.	.
				7	36	.	.
				8	50	.	.

Fig. 2 (cont'd)

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dox-guai	Compsition	5/10	9	58	.	.
			10	71	.	.
			11	76	.	.
			12	77	.	.
			13	90	.	.
			14	97	.	.
			15	101	.	.
			16	103	.	.
			17	108	.	.
			18	123	.	.
			19	131	.	.
			Total	N		
				Mean		
		7/10	1	22	.	.
			2	47	.	.
			3	111	.	.
			Total	N		
				Mean		
		10/10	1	23	.	.
			2	48	.	.
			3	53	.	.
			4	57	.	.
			5	67	.	.
			Total	N		
				Mean		
		Total	N			
			Mean			
		4/5/10	1	11	.	.
			Total	N		
				Mean		
			1	1	.	.
			2	32	.	.
			3	39	.	.

Fig. 2 (cont'd)

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MEDS	g-dox-gu	Composition	5/5/10	4	44	.	.
				5	51	.	.
				6	54	.	.
				7	62	.	.
				8	72	.	.
				9	85	.	.
				10	87	.	.
				11	93	.	.
				12	119	.	.
				13	129	.	.
				Total	N		
					Mean		
			Total	N			
				Mean			
	gab-dox	Composition	5/5	1	37	.	.
				2	65	.	.
				3	68	.	.
				Total	N		
					Mean		
			Total	N			
				Mean			
	k-ca-dox	Composition	10/4/5	1	86	.	.
				Total	N		
					Mean		
			Total	N			
				Mean			
			10/6/3	1	43	.	.
				Total	N		
					Mean		
				1	102	.	.

Fig. 2 (cont'd)

SUBSTITUTE SHEET (RULE 26)

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k-car-pi	Composition	10/4/3	2	104			
			Total	N	Mean		
		Total	N				
			Mean				
k-dox-ch	Composition	20/10/5	1	100			
			Total	N	Mean		
		Total	N				
			Mean				
k-dox-gu	Composition	3/5/5	1	6			
			Total	N	Mean		
		20/5/10	1	63			
			Total	N	Mean		
		Total	N				
			Mean				
k-dox-pi	Composition	10/4/3/5	1	122			
			Total	N	Mean		
		Total	N				
			Mean				
k-g-do-g	Composition	10/4/5/10	1	17			
			Total	N	Mean		
		Total	N				
			Mean				
k-gab	Composition	20/4	1	115		none	
			Total	N	Mean		1
		Total	N				.000
			Mean				.000
			1	117			

Fig. 2 (cont'd)

8/11

k-gab-am	Composition	20/5/5	Total	N			
				Mean			
k-gab-do	Composition	Total	N				
			Mean				
		20/4/5	1		55		
			Total	N			
				Mean			
		10/5/4	1		99	major	
			Total	N		1	
				Mean		3.000	
		10/5/5	1		113		
			Total	N			
				Mean			
		20/5/5	1		118		
			Total	N			
k-gab-gu	Composition	20/4/4/1	Total	N	Mean		
		20/5/5	1		105		
			Total	N			
				Mean			
		Total	N			1	
			Mean			3.000	
			1		94		
			Total	N			
				Mean			
			1		2		
			2		8	major	
			3		19		
			4		31		
			5		38		
			6		45	none	

Fig. 2 (cont'd)

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		k-gab-pi	Composition	10/4/3	7	56	.	.
					8	78	.	.
					9	89	.	.
					10	109	.	.
					11	120	.	.
					12	124	.	.
					13	130	.	.
					Total	N		2
						Mean		1.500
				10/4/1	1	16	.	.
					2	28	.	mild
					3	52	.	.
					4	66	.	.
					5	69	.	.
					6	75	moderate	.
					7	82	.	.
					8	84	.	.
					9	88	.	.
					10	91	.	.
					11	96	major	.
					12	125	.	.
					Total	N	2	1
						Mean	2.500	1.000
				10/1/3	1	114	.	.
					Total	N		
				Total	N		2	3
					Mean		2.500	1.333
	k-pi	Composition	10/3	1	127	.	.	
				Total	N			
					Mean			
				Total	N			
					Mean			
				1	110	.	.	

Fig. 2 (cont'd)

SUBSTITUTE SHEET (RULE 26)

10/11

la-li-gu	Composition	5/5/10	Total	N			
				Mean			
		Total	N				
			Mean				
lam-chl	Composition	7/10	1		3		moderate-major
			Total	N			1
				Mean			2.500
		10/10	1		24		
			2		70		
			3		106		
			Total	N			
				Mean			
		Total	N				1
			Mean				2.500
n-dox-ch	Composition	30/5/5	1		79		
			Total	N			
				Mean			
		Total	N				
Mean							
naproxen	Composition	30	1		60		
			Total	N			
		Total	N				
tri-chl	Composition	7/10	1		61		
			Total	N			
				Mean			
		7/13	1		92		
			2		107		
			Total	N			
				Mean			
		Total	N				
			Mean				

Fig. 2 (cont'd)

	Total	N		4	10
		Mean		2.500	1.400
June 2 1999 N=131					
a Limited to first 150 cases					

Fig. 2 (cont'd)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/14653

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61F 13/02
US CL : 424/447, 448, 449, 484; 514/78
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/447, 448, 449, 484; 514/78Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
GPI WEB CLIENT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P	US 5,837,289 A (GRASELA et al) 17 November 1998, see entire document.	1-53
Y, P	US 5,654,337 A (ROENTSCH et al) 05 August 1997, see entire document.	1-53
Y, P	US 5,885,597 A (BOTKNECHT et al) 23 March 1999, see entire document.	1-53

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A documents defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
13 SEPTEMBER 1999Date of mailing of the international search report
21 OCT 1999Name and mailing address of the ISA/US
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(12) **United States Patent**
Murdock et al.

(10) Patent No.: **US 6,479,074 B2**
(45) Date of Patent: ***Nov. 12, 2002**

(54) **METHODS AND TRANSDERMAL
COMPOSITIONS FOR PAIN RELIEF**

(75) Inventors: Robert W. Murdock, Selah, WA (US);
C. Donald Williams, Yakima, WA (US)

(73) Assignee: Pharmaceutical Applications
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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-
claimer.

(21) Appl. No.: 09/825,375

(22) Filed: Apr. 2, 2001

(65) Prior Publication Data

US 2002/0009487 A1 Jan. 24, 2002

Related U.S. Application Data

- (60) Division of application No. 09/652,662, filed on Aug. 31,
2000, and a division of application No. 09/342,679, filed on
Jun. 29, 1999, now abandoned, and a continuation-in-part of
application No. 09/106,684, filed on Jun. 29, 1998, now Pat.
No. 6,290,986, which is a continuation-in-part of application
No. PCT/US97/19651, filed on Oct. 24, 1997, and a con-
tinuation-in-part of application No. 08/957,485, filed on Oct.
24, 1997, now abandoned.
- (60) Provisional application No. 60/122,903, filed on Mar. 5,
1999, and provisional application No. 60/029,120, filed on
Oct. 24, 1996.

- (51) Int. Cl.⁷ A61F 13/00
- (52) U.S. Cl. 424/449; 424/447; 424/448;
424/484; 514/78; 514/906
- (58) Field of Search 424/447, 448,
424/449, 484; 514/906, 78

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(74) **Attorney, Agent, or Firm**—Lahive & Cockfield LLP;
Giulio A. DeConti; Maria C. Laccotripe

(57) **ABSTRACT**

The present invention features methods and compositions
for transdermal administration. In one embodiment, the
invention features methods and compositions for transder-
mal administration of an amine containing compound hav-
ing biphasic solubility and/or an agent which enhances the
activity of the amine containing compound having biphasic
solubility, e.g., a muscle relaxant, to relieve pain.

17 Claims, 11 Drawing Sheets

or 3800 Evaluation Management (pat. ver. 4.04-05) 00000000

Patent: _____ Date: _____

Current Medication: 1) _____
2) _____
3) _____
4) _____
5) _____

Diagnosis: Axis 1: _____ Axis 2: _____ Axis 3: _____

Subjective: _____

Objective: APPEARANCE: _____ APPETITE: _____
SPEECH: _____ COORDINATION: _____
MOOD: _____ VITALITY: _____
ANXIETY: _____ ANXIOUSNESS: _____
CYNICAL BELIEFS: _____ ENERGY LEVEL: _____
SLEEP: _____ WEIGHT: _____

SIDE EFFECTS: _____

RESPONSE OF DEPRESSION SYMPTOMS TO MEDICATIONS:
EXCELLENT: _____ GOOD: _____ POOR: _____ NA: _____

RESPONSE OF ANXIETY SYMPTOMS TO MEDICATIONS:
EXCELLENT: _____ GOOD: _____ POOR: _____ NA: _____

CONCURRENT MEDICATION CONDITIONS: _____

ADDITIONAL: _____

PLAN: 1) Continue with: _____
2) Change dosage: _____
3) New test: _____
4) _____

LAB STUDIES ORDERED: _____
OTHER: _____

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cpt 90862 Medication Management (cdw ver. 4-24-95)

90862.DOC

Patient: _____ Date _____

Current Medication: 1) _____
2) _____
3) _____
4) _____
5) _____
6) _____

Diagnoses: Axis 1: _____ Axis 3: _____
Axis 2: _____ GAF _____

Subjective: _____

Objective :	APPEARANCE _____	AFFECT _____
	SPEECH _____	CONCENTRATION _____
	MEMORY _____	IRRITABILITY _____
	APPETITE _____	AV HALLUC. _____
	CRYING SPELLS _____	ENERGY LEVEL _____
	SLEEP _____	WEIGHT _____

SIDE EFFECTS: _____

RESPONSE OF DEPRESSION SYMPTOMS TO MEDICATIONS:

EXCELLENT	GOOD	FAIR	POOR	N/A
-----------	------	------	------	-----

RESPONSE OF ANXIETY SYMPTOMS TO MEDICATIONS:

EXCELLENT	GOOD	FAIR	POOR	N/A
-----------	------	------	------	-----

CONCURRENT MEDICATION CONDITIONS: _____

ASSESSMENT: _____

PLAN: 1) Continue meds: _____
2) Change dosage: _____
3) New Med: _____
4) _____

LAB STUDIES ORDERED: _____

OTHER: _____

Fig. 1

Case Processing Summary(a)

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
ankle * MEDS * Composition	4	3.1%	127	96.9%	131	100.0%
arm * MEDS * Composition	10	7.6%	121	92.4%	131	100.0%
Back * MEDS * Composition	69	52.7%	62	47.3%	131	100.0%
elbow * MEDS * Composition	11	8.4%	120	91.6%	131	100.0%
headache * MEDS * Composition	131	100.0%	0	.0%	131	100.0%
Knee * MEDS * Composition	19	14.5%	112	85.5%	131	100.0%
hip * MEDS * Composition	15	11.5%	116	88.5%	131	100.0%
Neck * MEDS * Composition	28	21.4%	103	78.6%	131	100.0%
leg * MEDS * Composition	13	9.9%	118	90.1%	131	100.0%
shoulder * MEDS * Composition	25	19.1%	106	80.9%	131	100.0%
wrist * MEDS * Composition	26	19.8%	105	80.2%	131	100.0%
a Limited to first 150 cases						

P

				Case Number	ankle	arm
c-dox-gu	Composition	5/5/10	1	26	.	.
			2	33	.	.
			3	41	.	.
			4	59	.	.
			5	73	.	.
			6	80	.	.
		4/5/10	Total	N		
				Mean		
			1	98	.	.
			2	112	.	.
			Total	N		
				Mean		

Fig. 2A

		Total	N			
			Mean			
c-gab-do	Composition	5/5/5	1		34	.
			Total	N		
				Mean		
		Total	N			
			Mean			
carb	Composition	4	1		5	.
			Total	N		
				Mean		
		6	1		81	.
			Total	N		
				Mean		
		Total	N			
			Mean			
carb-ami	Composition	4/5	1		12	.
			2		40	.
			3		49	.
			4		64	.
			Total	N		
				Mean		
		Total	N			
			Mean			
carb-gab	Composition	4/4	1		27	. mild-moderate
			2		35	.
			3		126	. moderate
			Total	N		2
				Mean		1.750
		Total	N			2
			Mean			1.750
			1		4	. moderate
			2		13	.
			3		15	.

Fig. 2B

	dox	Composition	5	4	42	.	.
				5	46	.	none
				6	74	.	.
				7	95	moderate	.
				8	116	.	.
				9	121	.	.
				10	128	.	moderate
				Total	N	1	3
					Mean	2.000	1.333
			Total	N		1	3
				Mean		2.000	1.333
	dox-chl	Composition	7/13	1	10	.	.
				Total	N		
					Mean		
			5/10	1	21	.	.
				2	29	.	.
				3	30	.	.
				Total	N		
					Mean		
			7/10	1	83	.	.
				Total	N		
					Mean		
			Total	N			
				Mean			
				1	7	.	.
				2	9	.	.
				3	14	.	.
				4	18	.	.
				5	20	.	.
				6	25	.	.
				7	36	.	.
				8	50	.	.

Fig. 2C

dox-guai	Compsition	5/10	9	58	.	.
			10	71	.	.
			11	76	.	.
			12	77	.	.
			13	90	.	.
			14	97	.	.
			15	101	.	.
			16	103	.	.
			17	108	.	.
			18	123	.	.
			19	131	.	.
		Total	N			
			Mean			
		7/10	1	22	.	.
			2	47	.	.
			3	111	.	.
			Total	N		
		10/10	1	23	.	.
			2	48	.	.
			3	53	.	.
			4	57	.	.
			5	67	.	.
			Total	N		
			Mean			
		Total	N			
			Mean			
		4/5/10	1	11	.	.
			Total	N		
			Mean			
			1	1	.	.
			2	32	.	.
			3	39	.	.

Fig. 2D

MEDS	g-dox-gu	Composition	5/5/10	4	44	.	.
				5	51	.	.
				6	54	.	.
				7	62	.	.
				8	72	.	.
				9	85	.	.
				10	87	.	.
				11	93	.	.
				12	119	.	.
				13	129	.	.
				Total	N		
					Mean		
				Total	N		
					Mean		
	gab-dox	Composition	5/5	1	37	.	.
				2	65	.	.
				3	68	.	.
				Total	N		
					Mean		
				Total	N		
					Mean		
	k-ca-dox	Composition	10/4/5	1	86	.	.
				Total	N		
					Mean		
				Total	N		
					Mean		
				1	43	.	.
			10/6/3	Total	N		
					Mean		
				1	102	.	.

Fig. 2E

k-car-pi	Composition	10/4/3	2		104	.	.
			Total	N			
				Mean			
		Total	N				
			Mean				
k-dox-ch	Composition	20/10/5	1		100	.	.
			Total	N			
				Mean			
		Total	N				
			Mean				
k-dox-gu	Composition	3/5/5	1		6	.	.
			Total	N			
		20/5/10	1		63	.	.
			Total	N			
				Mean			
		Total	N				
			Mean				
k-dox-pi	Composition	10/4/3/5	1		122	.	.
			Total	N			
				Mean			
		Total	N				
			Mean				
k-g-do-g	Composition	10/4/5/10	1		17	.	.
			Total	N			
				Mean			
		Total	N				
			Mean				
k-gab	Composition	20/4	1		115	.	none
			Total	N			
				Mean			
		Total	N				
			Mean				
			1		117	.	.

Fig. 2F

k-gab-am	Composition	20/5/5	Total	N			
				Mean			.
k-gab-do	Composition	Total	N				
			Mean				
		20/4/5	1		55	.	.
			Total	N			
		10/5/4	1		99	major	.
			Total	N		1	
						3.000	
		10/5/5	1		113	.	.
			Total	N			
k-gab-gu	Composition	20/5/5	1		118	.	.
			Total	N			
		20/5/5	1				
			Total	N			
		Total	N			1	
			Mean			3.000	
		20/4/4/1	1		94	.	.
			Total	N			
		20/5/5	1		105	.	.
			Total	N			
		Total	N				
			Mean				
			1		2	.	.
			2		8	.	major
			3		19	.	.
			4		31	.	.
			5		38	.	.
			6		45	.	none

Fig. 2G

				10/4/3	7	56	.	.
					8	78	.	.
					9	89	.	.
					10	109	.	.
					11	120	.	.
					12	124	.	.
					13	130	.	.
					Total	N		2
						Mean		1.500
	k-gab-pi	Composition		10/4/1	1	16	.	.
					2	28	.	mild
					3	52	.	.
					4	66	.	.
					5	69	.	.
					6	75	moderate	.
					7	82	.	.
					8	84	.	.
					9	88	.	.
					10	91	.	.
					11	96	major	.
					12	125	.	.
					Total	N	2	1
						Mean	2.500	1.000
				10/1/3	1	114	.	.
					Total	N		
				Total	N		2	3
					Mean		2.500	1.333
	k-pi	Composition		10/3	1	127	.	.
					Total	N		
				Total	Mean			
					1	110	.	.

Fig. 2H

la-li-gu	Composition	5/5/10	Total	N			
			Mean				
		Total	N				
lam-chl	Composition	7/10	Mean				
			1		3	.	moderate-major
			Total	N			1
		10/10	Mean				2.500
			1		24	.	.
			2		70	.	.
			3		106	.	.
			Total	N			
			Mean				
		Total	N				1
			Mean				2.500
n-dox-ch	Composition	30/5/5	1		79	.	.
			Total	N			
			Mean				
		Total	N				
naproxen	Composition	30	1		60	.	.
			Total	N			
		Total	N				
tri-chl	Composition	7/10	1		61	.	.
			Total	N			
			Mean				
		7/13	1		92	.	.
			2		107	.	.
			Total	N			
			Mean				
		Total	N				
			Mean				

Fig. 2I

	Total	N		4	10
		Mean		2.500	1.400
June 2 1999 N=131					
a Limited to first 150 cases					

Fig. 2J

METHODS AND TRANSDERMAL COMPOSITIONS FOR PAIN RELIEF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to divisional application Ser. No. 09/652,662 filed Aug. 31, 2000, U.S. Pat. application No. 09/342,679 filed on Jun. 29, 1999, abandoned U.S. Provisional Patent Application No. 60/122,903 filed on Mar. 5, 1999, and is also a continuation-in-part of U.S. patent application Ser. No. 09/106,684 filed on Jun. 29, 1998, now U.S. Pat. No. 6,290,986 which is a continuation-in-part of PCT Application Ser. No. PCT/US97/19651 filed on Oct. 24, 1997, and a continuation-in-part of U.S. patent application Ser. No. 08/957,485 filed on Oct. 24, 1997, now abandoned, and U.S. Provisional Patent Application Ser. No. 60/029,120 filed on Oct. 24, 1996. The contents of all of the aforementioned application(s) are hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention is directed to methods and compositions for transdermal administration. In particular, the present invention is directed to methods and compositions for the transdermal administration of an amine containing compound having biphasic solubility and/or an agent which enhances the activity of the amine containing compound having biphasic solubility, e.g., a muscle relaxant, to relieve pain.

BACKGROUND OF THE INVENTION

It is believed that damage to somatic sensory nerves causes a somatic sensory loss. Such damage can be caused by a variety of means including trauma, diseases such as diabetes, herpes zoster and late-stage cancer, chemotherapy, or by a chemical injury. It is believed that neural pain circuits rewire themselves, both anatomically and biochemically, after nerve injury. In many patients suffering from damage to somatic sensory nerves, negative symptoms such as numbness are joined by positive sensations, involving a sort of false sensation of pain. The experience can range from mild dysesthesia to excruciating pain, rendering some patients unable to work, walk or do other daily activities.

In the past, patients were generally treated by administration of analgesics to relieve pain. A vast majority of such patients receive doses of these agents orally. Unfortunately, in some situations, oral administration of such agents has been associated with a variety of side effects, such as liver damage, kidney damage, gastrointestinal side effects, addiction, sedation, and/or weight gain which cannot be tolerated well by the patient. In other cases, malabsorption of oral preparations have resulted in subtherapeutic plasma levels. In other cases, the agents have relatively short plasma half-lives, necessitating inconveniently frequent dosing. In general, oral delivery involves a time delay as the analgesic is absorbed via the digestive system before entering the bloodstream. A number of agents which have traditionally been administered orally or by injection have been inappropriate or suboptimal for some patients when so-administered. There are a number of medications which, in at least some patients, are not tolerated well when orally administered (e.g. which cause undesirable gastrointestinal or other side effects) and/or which provide undesirably high or low concentrations or delayed concentrations in a target tissue. In some cases, dosages which are appropriate for oral administration, upon being distributed more or less uniformly throughout the body, are undesirably low in a par-

ticular area, e.g., tissue, to achieve desired results. Oral or injection administration may result in too slow or too rapid increase in blood plasma levels, e.g., may involve an undesirably long time delay as the analgesic is absorbed by the digestive system before entering the bloodstream, or may result in a "spike" in blood plasma levels followed by an undesirably low level, where a more constant level would be preferable. Some analgesics are particularly prone to cause or contribute to kidney or liver damage when administered orally.

Although other forms of delivery of pharmaceuticals agents are known, each has its drawbacks. Parenteral (i.e., intravenously or intramuscularly injected) administration is inconvenient and expensive, and is rarely used outside the hospital. Inhalation is believed to be not feasible with many analgesic agents currently in use. Therefore, there is a need for an analgesic delivery system which provides effective and acceptable levels, while preferably avoiding or reducing undesired effects such as liver damage or gastrointestinal side effects.

SUMMARY OF THE INVENTION

The present invention provides a transdermal composition for the treatment of pain in a subject, particularly a human subject. The transdermal composition for the treatment of pain in a subject includes an amine containing compound having biphasic solubility in an amount effective to treat pain in a subject and a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound, e.g., a lecithin organogel carrier. In a preferred embodiment, the transdermal composition further includes an agent which enhances the activity of the amine containing compound having biphasic solubility, e.g., a muscle relaxant, such as guaifenesin, chlorzoxazone, dantrolene sodium, metaxalone, carisoprodol, and combinations thereof. Preferably, the agent which enhances the activity of the amine containing compound having biphasic solubility, e.g., the muscle relaxant, also has a biphasic solubility.

In one embodiment of the present invention, the amine containing compound having biphasic solubility is an antidepressant compound, such as a tricyclic antidepressant compound, e.g., doxepin or trimipramine.

In another embodiment of the present invention, the amine containing compound having biphasic solubility is a sodium channel blocker, an anti-epileptic compound, or an anti-convulsant compound.

Another embodiment of the invention features a transdermal composition which includes an amine-containing compound as described herein and an anti-inflammatory compound, such as a nonsteroidal anti-inflammatory compound, e.g., celecoxib, etodolac, mefenamic acid, nabumetone, salsalate, naproxen, viox® and combinations thereof. Such a composition can further include an agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant such as guaifenesin.

In another aspect, the invention features a transdermal composition for the treatment of pain in a subject including an amine containing compound having biphasic solubility in an amount effective to treat pain in a subject; a muscle relaxant in an amount effective to enhance the activity of the amine containing compound having biphasic solubility; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound having biphasic solubility and the muscle relaxant.

In yet another aspect, the invention features a transdermal composition for the treatment of pain in a subject including

doxepin in an amount effective to treat pain in a subject; guaifenesin in an amount effective to enhance the activity of doxepin; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the doxepin and the guaifenesin.

Other aspects of the invention feature methods for treating pain in a subject in which the subject is contacted with a transdermal composition including an amine containing compound having biphasic solubility in an amount effective to treat pain in the subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound to thereby treat pain in the subject. In a preferred embodiment, the transdermal composition is applied to the skin of the subject.

Another aspect of the invention features a method for selecting a compound suitable for treating pain in a subject. The method includes transdermally administering an amine containing compound having biphasic solubility to a subject; and determining whether pain is treated in the subject to thereby select a compound suitable for treating pain in a subject. In a preferred embodiment, the method can further include modeling the compound using a computer equipped with a three-dimensional chemical structure modeling program; and determining whether the three dimensional chemical structure of the compound possesses sufficient characteristics to be useful as a sodium channel blocker, thereby selecting a compound suitable for treating pain in a subject.

In another aspect, the invention features a transdermal composition suitable for transdermal delivery, which includes a therapeutically effective amount of a pharmaceutical compound (e.g., a serotonin specific reuptake inhibitor, a mood stabilizing compound, a dopamine compound, a compound suitable for treating attention deficit hyperactivity disorder, a compound suitable for treating hypertension and akathisia, an analgesic compound, or a compound used in the treatment of impotence) and a pharmaceutically acceptable carrier suitable for transdermal delivery of the pharmaceutical compound, e.g., a lecithin organogel carrier.

In yet another aspect, the invention features a transdermal composition for treatment of pain in a subject which includes a compound capable of blocking afferent neuron transmission in an amount effective to block afferent neuron transmission in a subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the compound.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is an evaluation form used in evaluating an embodiment of the present invention.

FIG. 2 is a table depicting the results from clinical experiments using compositions of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a transdermal composition suitable for treatment of pain in a subject. The transdermal composition includes an amine containing compound having biphasic solubility in an amount effective to treat pain in a subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound having biphasic solubility.

As used herein, the term "subject" includes a mammal, such as a human, a horse, a pig, a cow, a mouse, a rat, a rabbit, or a goat. In preferred embodiment, the subject is a human.

As used herein, the term "pain" is art recognized and includes a bodily sensation elicited by noxious chemical, mechanical, or thermal stimuli, in a subject, e.g., a mammal such as a human. The term "pain" includes chronic pain, such as lower back pain; pain due to arthritis, e.g., osteoarthritis; joint pain, e.g., knee pain or carpal tunnel syndrome; myofascial pain, and neuropathic pain. The term "pain" further includes acute pain, such as pain associated with muscle strains and sprains; tooth pain; headaches; pain associated with surgery; or pain associated with various forms of tissue injury, e.g., inflammation, infection, and ischemia.

As used herein, the term "amine containing compound having biphasic solubility" includes compounds having at least one amine moiety and having sufficient lipid solubility (e.g., solubility in polar solvents such as ethanol, ethoxydiglycerol, ethoxydiglycol, chloroform, benzene, and the like) such that the compound passes through the stratum corneum, and has sufficient aqueous solubility to be active in the aqueous environment of the dermis and the underlying tissue.

Transdermal compositions of the present invention include an amine containing compound having biphasic solubility in an amount effective to treat pain in a subject. As used herein, the terms "amount effective to treat pain in a subject" and "effective amount" are used interchangeably herein and include an amount effective, at dosages and for periods of time necessary, to achieve the desired result, e.g., sufficient to treat pain in a subject. An effective amount of an amine containing compound or a pharmaceutical compound as defined herein may vary according to factors such as the disease state, age, and weight of the subject, and the ability of the amine containing compound or pharmaceutical compound to elicit a desired response in the subject. Dosage regimens may be adjusted to provide the optimum therapeutic response. An effective amount is also one in which any toxic or detrimental effects of the amine containing compound having biphasic solubility or pharmaceutical compound are outweighed by the therapeutically beneficial effects.

The transdermal compositions of the invention can further include an agent which enhances the activity of the amine containing compound having biphasic solubility. As used herein, an "agent which enhances the activity of the amine containing compound having biphasic solubility" includes an agent which enhances the pharmacological activity of the amine containing compound having biphasic solubility (e.g., the ability of the amine containing compound to treat pain), or enhances the transdermal delivery of the amine containing compound having biphasic solubility (e.g., the ability of the amine containing compound to cross the stratum corneum), or enhances both the pharmacological activity and the transdermal delivery of the amine containing compound. Examples of agents which enhance the activity of the amine containing compound having biphasic solubility, include muscle relaxants, described in further detail below.

As used herein, the term "transdermal" composition includes compositions capable of passing through the stratum corneum of a subject. The term transdermal further includes compositions capable of passing through the epidermis of a subject, compositions capable of passing through the dermis of a subject, and compositions capable of passing through the hypodermis of a subject. In preferred embodiments, the term transdermal includes compositions capable of passing through the skin of a subject and reaching the underlying tissues and organs.

As used herein, the term "transdermal delivery" includes delivery of, for example, a compound through the stratum

corneum of a subject. The term transdermal delivery further includes delivery of, for example, a compound through the epidermis of a subject, delivery of, for example, a compound through the dermis of a subject, and delivery of, for example, a compound through the hypodermis of a subject. In preferred embodiments, the term transdermal delivery includes delivery of, for example, a compound through the skin of a subject to the underlying tissues and organs.

The present invention further features a transdermal composition for treatment of pain in a subject which includes a compound capable of blocking afferent neuron transmission in an amount effective to block afferent neuron transmission in a subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the compound.

As used herein, the term "compound capable of blocking afferent neuron transmission" includes a compound which is capable of blocking the ability of an afferent neuron, i.e., a sensory neuron, to carry an impulse toward the central nervous system.

Various aspects of the invention are described in further detail in the following subsections:

Amine Containing Compounds Having Biphasic Solubility

Amine containing compounds having biphasic solubility for use in the transdermal compositions of the invention include antidepressant compounds, antiepileptic compounds, anticonvulsant compounds, and sodium channel blockers. As used herein, the term "antidepressant compounds" includes compounds capable of alleviating the symptoms of depression. Examples of antidepressant compounds include all tricyclic antidepressants (e.g., amitriptyline, dothiepin, or lofepramine), bupropion (sold under the trade name Wellbutrin), reboxetine (sold under the trade name Edronax), nefazodone (sold under the trade name Serzone) and trazone (sold under the trade name Desyrel). Antidepressant compounds are described in, for example, the 1998 SIGMA catalogue and the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, the contents of which are incorporated herein by reference.

In one embodiment of the present invention, the antidepressant compounds of the present invention contain a tricyclic moiety. Therefore, in a preferred embodiment, a transdermal composition of the present invention includes a tricyclic antidepressant compounds. Exemplary tricyclic antidepressants include adinazolam, amitriptylinoxide, amoxapine, clomipramine, demexiptiline, dimetacrine, dothiepin, doxepin, imipramine N-oxide, iprindole, lofepramine, melitracen, metapramine, noxiptilin, pizotyline, propizepine, quinupramine, tianeptine, and trimipramine. A particularly preferred tricyclic antidepressant for use in the compositions of the invention is doxepin.

Tricyclic antidepressant compounds are described in, for example, "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995), the contents of which are incorporated herein by reference.

Preferably, the tricyclic antidepressant compound is selected from the group consisting of doxepin, trimipramine, other tricyclics having biphasic solubility, and combinations thereof. When combined with other compounds, such as an agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant, and/or an anti-inflammatory compound, e.g., a nonsteroidal anti-inflammatory compound, as discussed below, the tricyclic antidepressant preferably constitutes from about 1% by weight (% by wt.) to about 30% by wt. of the total amount of the pharmaceutical, more preferably from about 3% by wt. to about 15% by wt., and most preferably from about 5% by wt. to about 13% by wt.

The amine containing compounds having biphasic solubility used in the transdermal compositions of the invention further include antiepileptic compounds. As used herein, the term "antiepileptic compound" includes compounds capable of alleviating the symptoms of epilepsy. Exemplary antiepileptic compounds for use in the compounds of the invention include lamotrigine, felbamate, and carbamazepine. Preferably, the antiepileptic compound is selected from the group consisting of lamotrigine, felbamate, carbamazepine, and combinations thereof. When combined with other compounds, such as an agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant, and/or an anti-inflammatory compound, e.g., a nonsteroidal anti-inflammatory compound as discussed below, the antiepileptic compound constitutes from about 1% by wt. to about 30% by wt. of the total amount of the pharmaceutical, more preferably from about 3% by wt. to about 20% by wt., and most preferably from about 5% by wt. to about 15% by wt. Antiepileptic compounds are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, and the "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995) the contents of which are incorporated herein by reference.

In another aspect of the present invention, the amine containing compounds having biphasic solubility of the present invention include anticonvulsant compounds. As used herein, the term "anticonvulsant compound" includes compounds capable of alleviating the symptoms of convulsion, i.e., the violent involuntary tetanic contractions of an entire group of muscles. Exemplary anticonvulsant compounds which for use in the compositions of the invention include felbamate, lamotrigine and carbamazepine. Preferably, the anticonvulsant compound is selected from the group consisting of felbamate, lamotrigine, and combinations thereof. When combined with other compounds, such as an agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant, and/or an anti-inflammatory compound, e.g., a nonsteroidal anti-inflammatory compound as discussed below, the anticonvulsant compound constitutes from about 1% by wt. to about 30% by wt. of the total amount of the pharmaceutical, more preferably from about 3% by wt. to about 20% by wt., and most preferably from about 5% by wt. to about 15% by wt. Anticonvulsant compounds are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, and the "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995) the contents of which are incorporated herein by reference.

In yet another aspect of the present invention, the amine containing compounds having biphasic solubility of the present invention include adrenergic agonist compounds. Preferably, the adrenergic agonist compound is tizanidine. When combined with other compounds, such as a muscle relaxant and/or nonsteroidal anti-inflammatory compound as discussed below, the adrenergic agonist compound constitutes from about 1% by wt. to about 30% by wt. of the total amount of the pharmaceutical, more preferably from about 3% by wt. to about 20% by wt., and most preferably from about 5% by wt. to about 15% by wt. Adrenergic agonist compounds are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, and the "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995) the contents of which are incorporated herein by reference.

The amine containing compounds having biphasic solubility used in the transdermal compositions of the invention further include sodium channel blockers. As used herein, the term "sodium channel blockers" includes compounds which are capable of blocking the activity of a sodium channel. Examples of sodium channel blockers include tetrodotoxin, flecainide, disopyramide, and terfenadine. Sodium channel blockers are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, and the "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995) the contents of which are incorporated herein by reference.

Whenever nerves are damaged, for example, by trauma, by diseases such as diabetes, herpes zoster, or late-stage cancer, or by chemical injury (e.g., as an untoward consequence of agents including the false-nucleoside anti-HIV pharmaceuticals), neural pain circuits rewire themselves, anatomically and/or biochemically. Thus, following an injury, new sodium channels are formed which is believed to constitute the basis for chronic pain development. Through a similar action in the dorsal root ganglia, chronic regional pain syndromes may develop. Each time one of these sodium channels depolarizes, a nerve impulse originates. Because there are so many sodium channels, there may be a constant cascade of nerve impulses, causing allodynia, burning sensations, and/or dysesthesias. It is believed that some chronic pains may be mediated through sodium channels in nerve cells. Thus, it is believed that amine containing compounds having biphasic solubility which can block sodium channels may also be used in the transdermal compositions of the invention.

In one embodiment of the invention, the amine moiety of the amine containing compounds having biphasic solubility of the present invention may function similar to a sodium ion upon entry into the sodium channel of a nerve cell membrane. A non-polar moiety, which is preferably present in the amine containing compound having biphasic solubility of the present invention may interact with the nerve cell membrane, perhaps through Van der Waals forces. In such cases, it is believed that the presence of the non-polar moiety prevents or inhibits a complete uptake of the amine containing compound having biphasic solubility through the nerve cell membrane. It is believed that one or more these interactions prevent or reduce the amount and/or the rate of depolarization and ion exchange involved in stimulus conduction, thereby decreasing pain sensation.

The amount of an amine containing compound having biphasic solubility useful in relieving pain transdermally may be determined by methods known in the art, and typically ranges from about 1 mg to about 300 mg per subject per dose, preferably from about 5 mg to about 100 mg per subject per dose, and more preferably from about 10 mg to about 50 mg per subject per dose, depending on a variety of factors including the particular amine containing compound having biphasic solubility used, whether the area of transdermal application is the site of action, and the intended size of the site of action. In a preferred embodiment, the amount of an amine containing compound having biphasic solubility useful in relieving pain transdermally, is 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 mg, 150 mg, 200 mg, 250 mg, or 300 mg per subject per dose.

Muscle Relaxants

Transdermal compositions of the present invention may also include a muscle relaxant. As used herein, the term "muscle relaxant" includes compounds which facilitate or

enhance the relaxation of muscles (e.g., provide relief from muscle spasm) and, thus, facilitate or enhance the transdermal delivery of the transdermal compositions of the invention. Exemplary muscle relaxants include both skeletal muscle relaxants and smooth muscle relaxants such as anticholinergics, antispasmodics, bronchodilators, and vasodilators. Muscle relaxants are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, pp. THER-1 to THER-28, and the "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995) the contents of which are incorporated herein by reference. Preferably, the muscle relaxant is selected from the group consisting of guaifenesin, benzodiazepines (e.g., clonazepam or diazepam), chlorzoxazone, dantrolene sodium, metaxalone, carisoprodol, other muscle relaxants having biphasic solubility, and combinations thereof. More preferably, the muscle relaxant is selected from the group consisting of guaifenesin, chlorzoxazone, and combinations thereof. A preferred muscle relaxant for use in the compositions of the invention is guaifenesin.

Preferably the muscle relaxant has biphasic solubility. Preferably the muscle relaxant, when present in the pharmaceutical composition, constitutes from about 1% by wt. to about 30% by wt. of the total amount of the pharmaceutical, more preferably from about 3% by wt. to about 20% by wt., and most preferably from about 5% by wt. to about 15% by wt.

Anti-Inflammatory Compounds

The transdermal compositions of the present invention may also include an anti-inflammatory compound. As used herein, the term "anti-inflammatory compound" includes a compound which is capable of reducing cell migration, caused by ischemic and trauma associated events, and therefore reduces edema formation to thereby provide pain relief. Preferably, the anti-inflammatory compound is a nonsteroidal anti-inflammatory compound (i.e., NTHE) including ketoprofen. Anti-inflammatory compounds, e.g., NTHEs, are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, pp. THER-1 to THER-28, and the "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995) the contents of which are incorporated herein by reference. Preferably, the NTHE is selected from the group consisting of celecoxib, etodolac, mefenamic acid, nabumetone, salsalate, naproxen, Vioxx®, COX-2 NTHEs having biphasic solubility, and combinations thereof.

More preferably, the NTHE is selected from the group consisting of celecoxib, etodolac, naproxen, COX-2 NTHEs having biphasic solubility, and combinations thereof. Preferably, the NTHE has biphasic solubility. The NTHE, when present in the transdermal composition, preferably, constitutes from about 1% by wt. to about 30% by wt. of the total amount of the pharmaceutical, more preferably from about 3% by wt. to about 30% by wt., and most preferably from about 5% by wt. to about 30% by wt.

Dosages

The concentration as well as the quantity of the amine containing compounds having biphasic solubility, the agents which enhance the activity of the amine containing compounds, e.g., the muscle relaxants, and the anti-inflammatory compounds can be varied independently in order to achieve the desired effect. For example, higher concentrations of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds contained in a dosage form of

decreased viscosity may result in an analgesic with fast onset and short duration. High concentrations of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds contained in a dosage form of increased viscosity may result in potent analgesic with fast onset and long duration. Low concentrations of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds in a dosage form of decreased viscosity may result in mild analgesic with longer onset and short duration. Low concentrations of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds contained in a dosage form of increased viscosity may have mild analgesic properties with longer onset and longer duration. The ability to vary the concentration of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds from very low to high of the total composition, combined with the ability to coat thin (about 0.1 mm) or thick (about 0.5 mm) enables the practitioner of the invention to vary the dosage of the system as needed for particular level of pain and anatomical sites of interest. It should be appreciated, however, that, onset time as well as duration of analgesic effect of the transdermal composition of the present invention will vary from subject to subject as well as on the basis of the site of application, and properties of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds.

Generally, the concentration of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds can range, on a weight basis, from about 1% to about 30% of the total composition, preferably from about 3% to about 20%, and more preferably from about 5% to about 15%.

Pharmaceutically Acceptable Carriers

The transdermal compositions of the present invention also includes a pharmaceutically acceptable carrier which is capable of transdermal delivery of the amine containing compound having biphasic solubility. As used herein, the term "pharmaceutically acceptable carrier suitable for transdermal delivery" includes a carrier capable of delivering the amine containing compound transdermally as defined above. Suitable carriers for transdermal delivery of pharmaceuticals are described in U.S. Pat. No. 5,446,070, the contents of which are incorporated herein by reference. Briefly, pharmaceutically acceptable carriers of the present invention include any suitable finite (i.e., solid) or non-finite (i.e., non-solid, such as liquid or semi-liquid) carrier including liquids, semi-liquids or solid carriers, such as a bioadhesive. Thus, the amine containing compounds having biphasic solubility may be admixed with a pharmaceutically acceptable carrier such as a cream, gel, emulsion, lotion, salve, paste, plaster, ointment, spray solution, or any other "non-finite" carrier known in the art of pharmaceutical delivery. For example, the base of a non-finite carrier may be lipid including phospholipids such as lecithins; fatty oils; lanolin; vasoline; paraffins; glycols; higher fatty acids; and higher alcohols.

The term "bioadhesive" as used herein includes an adhesive which attaches to a biological surface such as skin or mucosal tissue. Preferably, the bioadhesive of the present invention is self-adhesive in that it attaches to the site of interest without the need to reinforce its attachment by way of another adhesive. Suitable bioadhesive include natural or synthetic polysaccharides such as cellulose derivatives including methylcellulose, cellulose acetate,

carboxymethylcellulose, hydroxyethylcellulose and the like; pectin; a mixture of sulfated sucrose and aluminum hydroxide; hydrophilic polysaccharide gums including natural plant exudates, such as karaya gum, ghatti gum, tragacanth gum, xanthan gum, jaraya gum and the like; seed gums including guar gum, locust bean gum, psillium seed gum and the like; and lecithins such as soya lecithin. In addition to the above ingredients, compositions of the present invention may also include other ingredients such as various pharmaceutically acceptable additives available to those skilled in the art. These additives include binders, stabilizers, preservatives, flavorings, dyes, and pigments.

In another embodiment, the pharmaceutically acceptable carrier of the present invention includes van pen cream (cetyl alcohol, stearyl alcohol, steric acid, glycerol monostearate, isopropyl myristate, soya lecithin, BHT alcohol 95%, simethicone, sodium hydroxide 30% solution, polyoxyl stearate, edetate disodium 5%, purified water, urea).

Other Pharmaceutical Compounds

In another aspect, the invention features a transdermal composition suitable for transdermal delivery, which includes a therapeutically effective amount of a pharmaceutical compound (e.g., a serotonin specific reuptake inhibitor, a mood stabilizing compound, a dopamine compound, a compound suitable for treating attention deficit hyperactivity disorder, a compound suitable for treating hypertension and akathisia, an analgesic compound, or a compound used in the treatment of impotence) and a pharmaceutically acceptable carrier suitable for transdermal delivery of the pharmaceutical compound.

As used herein, the term "pharmaceutical compound" includes compounds suitable for treating a targeted condition and capable of being delivered in active form, in vivo. Examples of pharmaceuticals include drugs, enzymes, chemical compounds, combinations of chemical compounds, biological macromolecules and analogs thereof. Examples of pharmaceutical compounds are described in detail below.

In one embodiment of the invention, the pharmaceutical compound is a serotonin specific reuptake inhibitor (SSRI). SSRIs are commonly prescribed for patients with diagnoses of mood disorders, some forms of anxiety disorder (particularly panic disorder), obsessive compulsive disorders, some forms of menopausal disorders, and eating disorders (especially bulimia nervosa). Examples of such SSRIs include sertraline (sold under the trade name Zoloft), paroxetine (sold under the trade name Paxil), fluoxetine (sold under the trade name Prozac), venlafaxine (sold under the trade name Effexor), and fluvoxamine (sold under the trade name Luvox).

In another embodiment of the invention, the pharmaceutical compound is a mood stabilizing medication, such as carbamazepine (sold under the trade name Tegretol) and valproic acid (sold under the trade name Depakote). These agents are used frequently in psychiatric practice as either augmentation medications (to render antidepressants more effective) or as anti-manic medications in the treatment of bipolar mood disorder. Mood stabilizing medications are also used in neurologic practice for the treatment of seizure disorders and for the treatment of certain pain disorders.

In yet another embodiment of the invention, the pharmaceutical compound is a compound used for treating Attention Deficit Hyperactivity Disorder (ADHD), one example of which is permoline, sold under the trade name Cylert. Permoline is a medication that is used in the treatment of Attention Deficit Hyperactivity Disorder in children and

adults. It is practically insoluble in water, but soluble in ethylene glycol and lipids, making it a good candidate for transdermal administration

In a further embodiment of the invention, the pharmaceutical compound is a dopamine compound, used for treating Parkinson's disease, examples of which are pergolide, sold under the trade name Permax and bromocriptine mesylate, sold under the trade name Parlodel.

In yet another embodiment of the invention, the pharmaceutical compound is a compound used for treating hypertension and akathisia, one example of which is propranolol, sold under the trade name Inderal.

In yet a further embodiment of the invention, the pharmaceutical compound is a compound used in the treatment of impotence such as sildenafil, sold under the tradename Viagra. It is believed that transdermal administration of sildenafil may be useful, for at least some subjects, as compared to oral administration which has been found, in at least some situations, to be associated with gastrointestinal side effects.

Methods For Preparing The Transdermal compositions

Another embodiment of the present invention provides a method for preparing the above described transdermal compositions, by admixing a therapeutically effective amount of the amine containing compound having biphasic solubility, optimally an agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant, optimally an anti-inflammatory compound with the carrier suitable for transdermal delivery of the amine containing compound.

In one embodiment of the present invention, a transdermal composition is prepared by dispersing or dissolving crushed tablets, capsules or other preparation(s) of the amine containing compound having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds, which were intended for oral delivery, in a gel formed of soya lecithin and isopropyl palmitate or isopropyl myristate, alcohol, or ethoxy diglycol. In another embodiment of the present invention, Pluronic gel, formed of Pluronic such as Pluronic F127, potassium sorbate and water is used.

In a particular embodiment of the present invention, a transdermal composition including a combination of doxepin with guaifenesin is useful for treating pain. It is believed that transdermal administration of such combination can be advantageous, for at least some patients, as compared to oral administration, because higher local pharmaceutical concentrations at the site(s), e.g., of injury, can be achieved yielding an improved therapeutic response without systemic side effects such as weight gain, drowsiness, gastrointestinal upset and/or other known side effects of these pharmaceuticals.

Methods For Use

In one embodiment, the invention feature methods for treating pain in a subject in which the subject is contacted with a transdermal composition including an amine containing compound having biphasic solubility in an amount effective to treat pain in the subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound to thereby treat pain in the subject. In a preferred embodiment, the transdermal composition is applied to the skin of the subject as often as needed for the alleviation of pain. For example, the transdermal composition may be applied daily, weekly, monthly, yearly, for a length of time sufficient to alleviate pain.

Detailed examples of the preparation are provided below, along with examples of results obtained from transdermal administration to human patients. Preferably, a gel prepara-

tion is applied to the skin at the site or sites of pain. Patients can be evaluated by means of a structured evaluation form, e.g., completed at a frequency of at least one time per week. Evaluation of patients are for the present symptoms as well as any side effects from currently administered medications. This makes it possible to note changes on an ongoing basis.

Compositions of the invention can be self-administered doses in the form of a gel applied to the skin by the patient, or be implemented by providing a transdermal preparation in premeasured doses preferably in connection with an adhesive or other covering or patch so that the dosage may be administered e.g., by placing the adhesive patch on the skin of the patient. Although some embodiments of the invention have been described in connection with positioning the pharmaceutical gel on the arm of a patient, other positioning on the skin of a patient can also be used. Because, depending on the formulation, speed or duration of transdermal delivery may vary as function of skin location, in one embodiment the location of the skin to which the pharmaceutical is applied is selected so as to relatively increase or decrease the delay, speed, duration, or rate of delivery of the pharmaceutical, either with respect to a particular tissue or systemically.

For example, when a rapid rise in blood serum levels is desired, a placement which enhances delivery rate, such as behind the ear, can be used. When it is desired to enhance dose or delivery rate locally, the transdermal formulation may be positioned adjacent the desired treatment area. Membranes or matrices, such as a polymer matrix, may be used to limit or control delivery rates. In addition to transdermal gel or patch delivery, delivery of the transdermal or aerosol formulation can be achieved, e.g. by administration as nose drops, eardrops, eyedrops and/or suppositories.

In one embodiment, medications dispensed in transdermal gel form will be dispensed in unit doses, such as blister packs. The gel will be extruded from the blister pack, and rubbed on the administration site. The dosage will be adjusted by varying the number of unit dose applied. This will ensure accurate dosimetry and will avoid contamination of the gel.

Methods For Selecting A Compound Suitable For Treating Pain

In a further aspect, the invention features a method for selecting a compound suitable for treating pain in a subject. The method includes transdermally administering an amine containing compound having biphasic solubility to a subject; and determining whether pain is treated in the subject to thereby select a compound suitable for treating pain in a subject. In a preferred embodiment, the method can further include modeling the compound using a computer equipped with a three-dimensional chemical structure modeling program (e.g., Molecules-3D Professional Edition, version 2.60, copyright 1991-1998, Molecular Arts Corp., © 1994-1998 WCB/McGraw Hill); and determining whether the three-dimensional chemical structure of the compound possesses sufficient characteristics to be useful as a sodium channel blocker, thereby selecting a compound suitable for treating pain in a subject.

The effectiveness of the amine containing compound having biphasic solubility to treat pain can be tested in vitro or in vivo. An animal model for pain, e.g., such as the one described in Kral M. G. et al. (1999) *Pain* 81(1-2):15-24 can, for example, be used for testing such compounds.

This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application, as well as the Figures are incorporated herein by reference.

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EXAMPLES

Example 1

One hundred grams of lecithin soya (granular) and 0.66 grams sorbic acid NF-FCC powder) were dispersed in 100 grams (117 milliliters (mL)) of isopropyl palmitate NF and allowed to stand overnight. Approximately 220 milliliters of lecithin-isopropyl palmitate in a form of a liquid of a syrup consistency was formed.

Example 2

One hundred grams of lecithin soya (granular) and 0.66 grams sorbic acid (NF-FCC powder) is dispersed in 100 grams (117 milliliters) of isopropyl myristate NF and allowed to stand overnight. Approximately 220 milliliters of lecithin-isopropyl myristate in a form of a liquid of a syrup consistency was formed.

Example 3

A beaker was prepared by measuring to a volume of 100 milliliters. It was considered important to measure the volume accurately rather than using beaker markings. An amount of Pluronic F127 NF (20 grams for a 20 percent gel, 30 grams for a 30 percent gel, 40 grams for a 40 percent gel) was mixed with 0.3 grams potassium sorbate NF. Refrigerated purified water was added in an amount sufficient to bring the volume to 100 milliliters. When all of the granules had been wet the gel was refrigerated. Solution took place upon cooling, taking 12 to 24 hours. The resulting 100 milliliters of Pluronic gel was kept refrigerated, since the gel will solidify at room temperature.

Example 4

Nine grams of carbamazepine in tablet form was ground in mortar and pestle. 4.3 milliliters of ethoxy diglycol was added and mixed to form a creamy paste. 13.2 milliliters of soya lecithin was added and mixed until smooth. The resulting 24 cc of solution was put into a 60 cc syringe. About 36 cc Pluronic F127 gel 20 percent (made according to Example 3) was placed in another syringe. The material was mixed well between syringes to yield 60 cc of carbamazepine organogel having a strength of 150 milligrams (mg) per milliliter. In some cases, the mixture was run through an ointment mill to reduce particle size.

Example 5

Sixty 100 milligram tablets of bupropion were ground and strained to form a fine powder. The bupropion powder was dissolved in 30 cc purified water, placed in a filter and washed with 10 to 20 cc purified water. The filtrate was used to make a 20 percent Pluronic gel using the procedures from Example 3, substituting filtrate for an equivalent volume of water, and stored in a refrigerator. Thirteen milliliters of soya lecithin was mixed with one-half the bupropion Pluronic gel and mixed between syringes to form a first batch. Thirteen milliliters of soya lecithin was mixed with the second half of the bupropion Pluronic gel and mixed between syringes to form a second batch. To each batch was added sufficient Pluronic gel F127 (made according to example 3) to yield a total of two 60 cc batches of bupropion HCl organogel having a strength of 15 milligrams per milliliter.

Example 6

600 milligrams of fluoxetine HCl (in the form of thirty 20 milligram capsules) was placed in a beaker and dissolved in

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approximately 18 cc of 95 percent ethyl alcohol. The solution was filtered through a filter funnel using fine filter paper. The residue was washed with 95 percent alcohol. The filtrate was heated, maintaining a temperature less than 85° C., to evaporate the alcohol to concentrate to 1 to 2 milliliters. 600 milligrams of isopropyl palmitate was combined with 600 milligrams of soya lecithin (granular), set aside and allowed to liquefy. Upon liquefaction, a thick syrupy consistency was obtained. 1.2 grams of the mixture was drawn into a 10 milliliter syringe and the alcoholic solution of fluoxetine HCl was drawn into another syringe. The two syringes were attached together with a Luer-Luer adapter and the gel was thoroughly mixed. All of the organogel was then transferred into one syringe and the empty syringe was disconnected. Sufficient quantity of 20 percent Pluronic F127 gel (formed as described in Example 3) was drawn into the empty syringe to make a total of 6 milliliters when added to the volume in the other syringe. A Luer-Luer adapter was attached and the contents of the two syringes was remixed until a smooth creamy mixture was obtained. All the mixture was transferred into one syringe, the empty syringe was removed and the Luer-Luer adapter was removed.

A Luer-oral adapter was attached to the mixture and transferred to six 1 milliliter oral syringes, was filled with 1 milliliter of the gel. In this way, each syringe contained five 20 milligram doses, or ten 10 milligram doses to yield a total of 60 doses of fluoxetine in lecithin organogel having a strength of 10 milligrams per 0.1 milliliters.

Example 7

Twelve 250 milligram tablets of nefazadone were crushed in a mortar and pestle and put through a strainer. 4.8 milliliters of ethoxy diglycol (8 percent) was added and mixed. In cases in which all particles were not dissolved, 2 milliliters of Pluronic were added and mixed. 13.6 milliliters of soya lecithin were added and mixed. The resulting mixture was put into syringes with a Luer adapter and mixed well. Sufficient Pluronic F127 gel, prepared according to Example 3, was added to achieve a volume of 60 cc and mixed well to yield 60 cc of nefazadone organogel having a strength of 50 milligrams per milliliter.

Example 8

Thirty 40 milligram tablets of paroxetine were crushed and run through a strainer, discarding green coating material. 4.8 milliliters of ethoxy diglycol was added to the powder and mixed in a mortar and pestle. Forty milliliters of Pluronic F127 gel 20 percent, formed according to Example 3, was added in graduated amounts to the powder and mixed until smooth using a spatula. 13.2 milliliters of soya lecithin was added and mixed well and the resulting material placed into syringes and sufficient quantity of Pluronic gel was added to bring the volume to 60 milliliters. In those such cases where particle size of the resulting material was too large, the cream was run through an ointment mill to yield 60 milliliters of paroxetine organogel having a strength of 20 milligrams per milliliter.

Example 9

Thirty 100 milligram tablets of sertraline were crushed into a fine powder and strained, discarding the yellow coating. Sufficient amount of Pluronic F127 gel 20 percent (formed according to Example 3) was added to achieve a volume of 38 milliliters and mixed well in a mortar and pestle until a smooth cream was achieved. This material was placed into syringes and mixed between the syringes to

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obtain a compact cream. 13.2 milliliters of soya lecithin was added and mixed well between the syringes using about 20 pumps. Sufficient quantity of Pluronic F127 gel 20 percent was added to yield 60 milliliters of sertraline gel having a strength of 15 milligrams per milliliter.

Example 10

Venlafaxine hydrochloride has a solubility in water of 572 mg/mL (adjusted to ionic strength of 0.2 M with sodium chloride). Forty-five 100 milligram tablets of venlafaxine were crushed and put through a strainer. The powder was dissolved in 15 cc purified water, the solution placed into a filter and washed with 10 cc purified water. The filtrate was used to make a 20 percent Pluronic gel using the procedures of Example 3 (substituting the filtrate for an equivalent amount of water) and placed into a refrigerator overnight. 13.2 milliliters of soya lecithin were drawn into a syringe with a Luer loc. The venlafaxine Pluronic gel was drawn into another syringe coupled to the first syringe and mixed well. Sufficient Pluronic F127 gel was added to achieve a volume of 60 cc with a strength of 75 mg. per cc.

Example 11

15 grams of sodium valproate (Depakote) was ground in mortar and pestle. 4 mL of ethoxy diglycol was added and mixed well to form a creamy paste. 19.8 mL of soya lecithin was added and mixed until smooth. The resulting 24 cc of solution was put into 2 syringes with a Luer Loc and mixed well. The mixture was divided so that half is in each syringe. Using another 60 cc syringe, Pluronic 30% gel was added to each to bring each syringe to a volume of 45 mL.

Example 12

Paroxetine hydrochloride has a solubility in water of 5.4 mg/mL. Paroxetine (Paxil) gel was prepared, according to the procedures of example 8. A dosage of 40 mg per day was self-administered by a 59 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 210 days, blood was drawn and blood serum level of Paxil was determined to be 0 nanograms (ng) per mL, while typical reference levels are 49±26 ng/mL, indicating possible poor absorption or lab error. Clinical evaluation of the patient over a 210 day period of such transdermal administration indicated benefit to patient without GI side effects similar to that noted with oral preparation.

Example 13

Sertraline hydrochloride is slightly soluble in water and isopropyl alcohol and sparingly soluble in ethanol. Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 100 mg per day was self-administered by a 54 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 19 days, blood was drawn and blood serum level of Zoloft was determined to be 5 ng/mL, while typical reference levels are 30–200 mg/mL indicating possible limited absorption or lab error.

Example 14

Fluoxetine hydrochloride has a solubility in water of 14 mg/mL. Fluoxetine (Prozac) gel was prepared, according to the procedures of example 6. A dosage of 20 mg per day was self-administered by a 54 year old female patient by application to the skin, for a period of at least 1 hour. No skin

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irritation was reported. After 7 days, blood was drawn and blood serum level of fluoxetine was determined to be 45 ng/mL, while the plasma level of the primary active metabolite norfluoxetine was also 45 ng/mL. There was evidence of patient benefit from the clinical evaluation.

Example 15

Carbamazepine is practically insoluble in water and soluble in alcohol and in acetone. Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 400 mg per day was self-administered by a 55 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 120 days, blood was drawn and blood serum level of Tegretol was determined to be 4.6 micrograms (μ g) per mL, while typical therapeutic levels are 4–10 11 μ g/mL indicating good absorption. There were no GI side effects and the patient demonstrated clinical improvement.

Example 16

Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 200 mg per day was self-administered by a 53 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 60 days, blood was drawn and blood serum level of Tegretol was determined to be 10.8 μ g/mL, while typical therapeutic levels are 4–10 11 μ g/mL indicating excellent absorption. There were no GI side effects and the patient demonstrated clinical improvement.

Example 17

Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 50 mg per day was self-administered by a 53 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 63 days, blood was drawn and blood serum level of Zoloft was determined to be 23 ng/mL, while typical reference levels are 30–200 mg/mL. The patient demonstrated a good clinical response without GI side effects.

Example 18

Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 200 mg per day was self-administered by a 47 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 91 days, blood was drawn and blood serum level of Tegretol was determined to be less than 0.5 μ g/mL, while typical therapeutic levels are 4–10 μ g/mL, indicating poor absorption, lab error, or patient non-compliance.

Example 19

Bupropion is highly soluble in water. Bupropion (Wellbutrin) gel was prepared, according to the procedures of example 5. A dosage of 100 mg per day was self-administered by a 47 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 44 days, blood was drawn and blood serum level of Wellbutrin was determined to be less than 0.5 ng/mL, while typical therapeutic levels are 10–30 indicating poor absorption, lab error, or patient non-compliance.

Example 20

Fluoxetine gel was prepared, according to the procedures of example 6. Typically, a total daily adult dosage of

fluoxetine as applied to the skin according to the present invention is between about 20 mg and 200 mg, more preferably between about 120 mg and about 200 mg. Dosages for non-adults and/or non-human mammals may need to be adjusted, e.g. proportionally to body weight. A dosage of 20–60 mg per day was self-administered by 5 patients, including that of example 13 and also including a 44 year old male patient, a 53 year old female patient, a 47 year old male patient and a 36 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 30–180 day period of such transdermal administration indicated a clinical response ranging from complete remission of symptoms to moderate improvement.

Example 21

Fluoxetine gel was prepared, according to the procedures of example 6. A dosage of 80–160 mg per day was self-administered by a 50 year old female by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7 days at the 80 mg dosage level blood was drawn and the blood serum of fluoxetine was determined to be 34 ng/mL fluoxetine and 25 ng/mL norfluoxetine, while typical reference levels are 50–480 ng/mL, indicating good absorption. There was evidence of patient benefit from the clinical evaluation. The dosage was then increased to 160 mg per day and administered by the same method. After 7 days at the 160 mg dosage level blood was drawn and the blood serum level of fluoxetine was determined to be 90 ng/mL fluoxetine and 25 ng/mL norfluoxetine, indicating good absorption. There was evidence of increased patient benefit at this higher dosage level which correlated positively with the higher plasma level. The patient has been receiving the medication continuously for a period of 5 months.

Example 22

Fluoxetine gel was prepared, according to the procedures of example 6. A dosage of 80–160 mg/day was self-administered by a 38 year old female by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7 days at the 80 mg dosage level, blood was drawn and the blood serum level of fluoxetine was determined to be 25 ng/mL of fluoxetine and 25 ng/mL norfluoxetine. There was evidence of patient benefit from the clinical evaluation. The dosage was then increased to 160 mg per day and administered by the same method.

Example 23

Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 50–200 mg per day was self-administered by 6 patients, including those of examples 12 and 16 and also including a 60 year old male patient, a 53 year old male patient, a 48 year old male patient, a 38 year old male patient and a 47 year old male patient, by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 7–90 day period of such transdermal administration indicated responses ranging from complete resolution of depression to no noticeable response.

Example 24

Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 200–400 mg per

day was self-administered by 6 patients, including those of examples 14, 15 and 17, and also including a 48 year old female patient, a 48 year old male patient and a 54 year old female patient, by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. The clinical evaluation of the patients over a 30–300 day period of such transdermal administration indicated responses ranging from moderate improvement to no positive clinical response.

Example 25

Paroxetine (Paxil) gel was prepared, according to the procedures of example 8. A dosage of 20 mg per day was self-administered by the patient of example 12 as well as by a 15 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. Clinical evaluation of the patients over a 30–210 day period of such transdermal administration indicated equivocal clinical improvement of the depression which may (or may not) have been related to the transdermally administered Paxil.

Example 26

Five 150 mg tablets of amitriptyline were crushed and run through a strainer. The powder was put into syringes with a Luer Loc and mixed well with 2 mL ethoxy diglycol. About 6 mL Pluronic Gel 20% was added and mixed well. 6.6 mL Soya Lecithin was added and mixed well. This mixture was thinned to 30-mL total volume with Pluronic Gel 20% and mixed well. The resulting mixture having a strength of 25 mg/mL was placed in appropriate dispensing device.

Example 27

Amitriptyline (Elavil) gel was prepared, according to the procedure of example 26. A dosage of 25 mg per day was self-administered by a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 100 day period of such transdermal administration indicated an apparently good clinical response, comparable to that achieved with oral medication.

Example 28

Trazodone (Desyrel) gel was prepared, according to a procedure similar to that of example 7. A dosage of 50–150 mg per day was self-administered by 2 patients, including a 36 year old female patient and a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 42–90 day period of such transdermal administration indicated a good to excellent clinical response.

Example 29

Venlafaxine (Effexor) gel was prepared, according to a procedure similar to that of example 9. A dosage of 150–225 mg per day was self-administered by 2 patients, including a 54 year old female patient and a 55 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 15–165 day period of such transdermal administration indicated a response ranging from no clinical improvement to mild clinical improvement.

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Example 30

Propranolol (Inderal) gel was prepared, according to a procedure similar to that of example 8 to produce a gel having a strength of 40 mg of propranolol per mL of gel. A dosage of 80 mg per day was self-administered by 2 patients, including a 36 year old female patient and a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 100 day period of such transdermal administration indicated results comparable to those achieved with oral medication.

Example 31

Bupropion (Wellbutrin) gel was prepared, according to a procedure described in example 5. A dosage of 150–200 mg per day was self-administered by 3 patients, including that of example 18, and also including a 38 year old male patient and a 53 year old female patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 5–45 day period of such transdermal administration indicated equivocal results.

Example 32

Valproic acid (Depakote) gel was prepared, according to a procedure similar to that of example 4. A dosage of 1000 mg per day was self-administered by a 38 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 30 day period of such transdermal administration indicated results comparable to those achieved with oral medication.

Example 33

Valproic acid (Depakote) gel was prepared according to the procedure of example 11. A dosage of 500–1000 mg was self administered by two male patients, ages 41 and 49. Administration was by application to the skin, for a period of at least one hour. Significant skin irritation occurred with one patient, but no gastrointestinal side effects were reported. Clinical evaluation of the patients over a period of two months revealed improvement, but upon longer term follow-up it appeared that other factors may have been responsible. After 28 days, blood was drawn and a serum valproic acid level of 26 $\mu\text{g/mL}$ was obtained for the 49 year old patient (while taking 250 mg twice daily), with a therapeutic reference range of 50–150 $\mu\text{g/mL}$. This indicated poor to fair absorption, and the dosage was raised to 500 mg twice daily, with a further improvement in clinical response. The 41 year old patient reported a good clinical response to an initial dosage of 250 mg adored twice daily, but a serum valproic acid level of only 1 $\mu\text{g/mL}$ was obtained. The dosage was increased to 500 mg twice daily, and a similar serum valproic acid level was obtained. The disparity between the clinical response and the plasma level might be explained either by laboratory error or placebo effect.

Example 34

A gel containing reboxetine (sold under the trade name Edronax) is prepared according to a procedure similar to that described in example 5 but using reboxetine in place of bopropion. The resulting mixture will be self administered by patients by application to the skin for a period of at least 1 hour. No skin irritation or gastrointestinal side effects are expected. Clinical evaluation of patients over a 5–45 day period of such transdermal administration is expected to indicate a good response to treatment.

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Example 35

Nefazodone (Serzone) gel was prepared, according to a procedure described in example 7. A dosage of 100 mg per day was self-administered by a 61 year old (male, female) patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 21 day period of such transdermal administration indicated a good response to treatment.

Example 36

1 gram of permoline tablets are crushed in a mortar and then dissolved in propylene glycol, just sufficient to effect dissolution. 3 mL of propylene glycol or 95% ethyl alcohol is added to form a paste. 6.6 mL soya lecithin is added to the mixture in the mortar. The mixture is placed in two syringes with a Luer Loc and mixed thoroughly. Each syringe is filled to 30 mL Pluronic F127 20% gel and mixed between syringes to produce a mixture having a strength of 33 mg/mL. The mixture is put in an appropriate dispensing device.

Example 37

A 16-year-old female with an established diagnosis of Attention Deficit Disorder had been treated successfully with oral pemoline (Cylert) for about 6 months. To potentially decrease the risk of liver damage associated with long-term use, permoline prepared according to the procedure of example 36 will be administered transdermally, by application to the skin in the post auricular region for a period of at least one hour, at two sites, twice daily. No skin irritation is expected. The clinical results are expected to be comparable to those obtained with the oral medication, although the dosage may have to be adjusted upwards to achieve adequate plasma levels, and more time may be required to achieve satisfactory plasma levels.

For psychiatric patients, some have received two or more psychopharmaceuticals, and in some cases, two or more of the above examples describe different evaluations for the same period of administration of a psychopharmaceutical agent.

Of the patients who have received prescriptions for one or more of the medications as described in the examples above, each had previously demonstrated a significant intolerance to oral administration of one or more medications, prior to instituting transdermal administration. The laboratory measures of plasma blood levels described above for transdermally administered fluoxetine and carbamazepine are believed to demonstrate good absorption transdermally using lecithin organogel matrix as the vehicle. Valproic acid and sertraline do not appear to be absorbed well or reliably. Valproic acid appears to cause skin irritation in some patients necessitating discontinuation. Both the laboratory measure of Bupropion and the patient clinical responses indicated poor or equivocal absorptions and results. Patient tolerance of transdermal administration has been good to excellent. Patients in the example above who suffered very severe GI side effects using oral preparations were more tolerant of the inconvenience of rubbing on the gel than were patients who had experienced only mild to moderate side effects. In general, more highly motivated and treatment-compliant patients also had a higher rate of sustained compliance.

Patients in the examples above were evaluated by means of a structured evaluation form depicted in FIG. 1, which was completed at a frequency of at least one time per week for each patient receiving transdermal medication according to the present invention. The patients were evaluated both

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for all present psychiatric symptoms as well as any side effects from currently-administered medications. In general, it is believed that patients with the most clear cut and uncomplicated diagnosis of major depression experienced the best results. In general, patients with severe personality disorders or with concealed substance abuse disorders did less well.

Example 38

1800 mg of gabapentin in powder form is dissolved with 1 mL propylene glycol in syringes with a Luer Loc. 6.6 mL of Soya lecithin is added and mixed thoroughly between syringes. The resulting material is placed in a device for dispensing measured amounts.

Example 39

Gabapentin mixtures of 2% and 4% will be prepared by substituting 1200 mg gabapentin or 600 mg gabapentin in place of 1800 mg gabapentin, in example 38.

Example 40

Gabapentin, prepared according to Example 38 or 39, will be combined with either 3% or 5% Lidocaine in varying ratios.

Example 41

4% gabapentin, prepared according to Example 38 or 39, will be combined with 7% carbamazepine and 7% amitriptyline.

Example 42

2% gabapentin, prepared according to Example 38 or 39, will be combined with 2% carbamazepine and 1% Piroxicam, which is expected to yield better penetration into muscle tissue.

Example 43

Gabapentin, prepared according to Example 38 or 39, in concentrations ranging from 2%–6% will be combined with clonidine in concentrations between 0.2% and 0.3%.

Example 44

A 56-year-old woman had pill upper and lower extremity spasms as a result of spastic quadriparesis resulting from an injury. Oral gabapentin, an anticonvulsant, had been administered previously, but had caused a "drugged" feeling, one of the commonly reported side effects with this agent. It was believed that use of transdermal gabapentin might provide local relief by achieving high local tissue concentrations near the site of administration without correspondingly elevated blood plasma levels. It is known that other anticonvulsants, such as carbamazepine, are useful in reducing neurogenic pain. Gabapentin's solubility in water exceeds 10%, making systemic absorption less likely. Gabapentin prepared according to the procedure of example 38 was self-administered by application to the skin in the area of pain. The patient reported moderate relief of spasms over a period of one week, with no systemic side effects and no report of skin irritation.

Example 45

Six grams of amitriptyline powder was placed in 40 milliliters of Pluronic F127 33% gel and placed under refrigeration to dissolve. Two milliliters of ethoxy diglycol

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was added to 4.8 grams of carbamazepine and mixed to form a smooth paste. 16.4 grams of soya lecithin was added to the resulting paste and mixed well. The dissolved amitriptyline composition was added to the carbamazepine composition and sufficient Pluronic F127 20% was added to make 120 milliliters and the resulting composition was mixed well to yield a composition having 5% amitriptyline and 4% carbamazepine.

Example 46

6 grams of doxepin was added to 20 milliliters Pluronic 33% F127 and put into a refrigerator to dissolve. 24 grams of ketoprofen and 12 grams of guaifenesin was added to 10 milliliters of 95% alcohol and mixed well. 26.4 milliliters of soya lecithin was added and mixed well and the doxepin composition was mixed with the ketoprofen/ guaifenesin composition. The resulting mixture was added to sufficient Pluronic 33% to yield 120 milliliters. The resulting composition was mixed well to yield a composition having about 20% ketoprofen, 5% doxepin and 10% guaifenesin

Example 47

6 grams of doxepin was added to 26 milliliters Pluronic 33% and refrigerated to dissolve. 2 milliliters ethoxy diglycol was added 4.8 grams carbamazepine and mixed. The resultant mixture was added to 24 grams ketoprofen and six milliliters alcohol and the result was mixed well. 26.4 milliliters soya lecithin was added to the ketoprofen composition and mixed well. The doxepin composition was mixed with the carbamazepine/ketoprofen composition and sufficient Pluronic 33% was added to yield 120 milliliters. The resultant composition was mixed well to yield a composition having about 20% ketoprofen, 4% carbamazepine and 5% doxepin.

Example 48

0.15 grams sildenafil was crushed and strained and dissolved in 5 milliliters Pluronic 20% F127 and mixed between syringes. 2.2 milliliters of soya lecithin was added and mixed. Sufficient Pluronic 20% was added to yield 10 milliliters and the resultant composition was mixed well to yield a composition having the strength of about 15 milligrams per milliliter.

Example 49

A mixture of Sildenafil 15 mg/ml was applied to the penis and scrotum of a 51 year old male. An immediate and strong erection resulted with sexual stimulation, without any irritation or burning. It is believed the composition will possess the therapeutic results claimed for orally administered Sildenafil, without any time delay, without any systemic GI side effects, and possibly without the degree of drug interaction with nitrates used in cardiac disease. It is believed that this will contribute both to the convenience of use of the pharmaceutical and to its safety.

Example 50

Compositions according the examples 45 through 47, 53, 55 were transdermally applied to numerous patients, for the purpose of treating pain including as described in other examples herein, with the results summarized in Table I below. The meaning of certain entries in Table I is indicated in Table II below. Blank results indicate no treatment at the pertinent site for this patient. Where a given line of Table I shows more than one site, one "best" (greatest pain relief) result if shown in bold.

TABLE I

Pa- tient	Age	Gen- der	Sur- gery	Pain	Keto- profen	Medication										Result																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																							
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						Gabapentinm	Piroxicam	doxepin	carbamazepine	amitriptyline	guifenesin	Dur- ation	shoul- der	back	neck	elbow	Knee	Wrist	Arm	Ankle	Hip	Leg																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																	
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TABLE I-continued

[illegible]

TABLE II

Gender: 1 = male	2 = female	
Surgery: 1 = one or more surgeries	2 = no surgeries	
Pain: 1 = mild	2 = moderate	3 = severe-sufficient to produce observed tears
Duration: length of treatment trial in weeks		
Result: 0 = no benefit		
1 = mild benefit		
2 = moderate benefit (greater than 25% pain reduction)		
3 = major benefit (greater than 40-45% pain reduction)		
4 = almost complete relief (greater than 80% pain reduction)		

Certain results drawn from the information of Table I are summarized in Table III and IV.

TABLE III

Percent reported pain relief						
Site	N (Number of data points)	None	Mild	Mild-moderate	moderate	Major
Wrist	13	16.7	33.3	8.3	41.7	
Shoulder	14	7.1	21.4	14.3	42.9	7.1
Elbow	5		40	20	20	20
Back	25	24	32	8	28	8
Arm	7	28.6	14.3	14.3	28.6	14.3
Neck	11	9.1	18.2		45.5	9.1
Knee	13	15.4	46.2	15.4	7.7	15.4

TABLE IV

(percent reported pain relief)							
	N	None	Mild	Mild-moderate	moderate	Major	Total
Best result without tricyclic	36	16.7	36.1	8.3	27.8	8.3	2.8
Best result with any tricyclic	20	10	10	20	35	15	10
Either tricyclic -sole agent	7		14.3	14.3	42.9	14.3	14.3
Best result with ketoprofen	25	16	44	4	28	8	
gabapentin piroxicam							
Best result without doxepin	43	18.6	32.6	14	23.3	7	4.7
Best result with doxepin	13		7.7	7.7	53.8	23.1	7.7

Example 51

A 51 year old female administered a composition prepared according to example 46, containing 20% ketoprofen, 5% doxepin, and 10% guaifenesin to her back for a period of 2 weeks. She reported moderate pain relief, lasting several hours, after each application. She reported no skin irritation nor any other side effects. Oral medications had produced no relief, and had caused significant GI side effects.

Example 52

A 34 year old man administered a composition containing 20% ketoprofen, 4% carbamazepine, and 5% doxepin to a very severely scarred wrist that had undergone 4 surgeries for carpal tunnel syndrome. He reported moderate pain relief, lasting for several hours after each application. No other treatment, including opiate oral pain medication, had been effective in providing even minor pain relief.

Example 53

24 grams ketoprofen and sufficient guaifenesin to result in a 10% final guaifenesin concentration, was mixed well with

10 milliliters 95% alcohol. 1200 mg gabapentin was dissolved in one ml propylene glycol in a syringe with a luer loc. 26.4 ml of soya lecithin was added to the ketoprofen-guaifenesin-alcohol mixture and mixed well. The resulting mixture was added to the gabapentin-propylene glycol mixture and mixed well. 4.8 gm of carbamazepine was combined with the resultant combination and mixed well to form a smooth paste. The resulting paste was combined with the ketoprofen-guaifenesin-alcoholgabapentin mixture and mixed well with sufficient pluronic to yield 120 ml of a composition containing ketoprofen 20%, carbamazepine 4%, gabapentin 4%, guaifenesin 10%.

Example 54

A 58 year old female with damage to her cervical spinal cord with a resultant spastic quadraparesis reported moder-

ate relief of both pain and muscle spasms when she applied a mixture prepared generally according to example 53, containing ketoprofen 20%, carbamazepine 4%, gabapentin 4%, guaifenesin 10% for a period of 8 weeks to her back and hip. She had been unable to tolerate both oral carbamazepine and oral gabapentin because of systemic side effects, including skin rash with the carbamazepine and dizziness and sedation with the gabapentin. She experienced no skin irritation nor other side effects with the transdermal formulation.

Example 55

Six grams of doxepin powder combined with 26 milliliters pluronic and placed in the refrigerator until dissolved. 1200 mg gabapentin was mixed with 1 ml propylene glycol and placed in a syringe with luer lock. 6.6 ml of soya lecithin was added and mixed well between syringes. 24 gm of ketoprofen and 8 milliliters alcohol was mixed well between two syringes with luer loc. The doxepin mixture was mixed well with the gabapentin mixture and subsequently the ketoprofen mixture was added and mixed well. Sufficient pluronic 20% (about 54 ml) was added to yield 60 ml of a

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composition having about 20% ketoprofen, 4% weight percent gabapentin and 5% weight percent doxepin.

Example 56

A 57 year old female applied a mixture, prepared generally according to example 55, containing ketoprofen 20%, gabapentin 4%; and doxepin 5% for a period of 8 weeks to her neck and reported major relief. She applied the same mixture to her shoulder and reported moderate relief. A mixture that substituted piroxicam for the doxepin produced only mild shoulder relief.

Example 57

A 35 year old man with a history of knee injury with vascular compromise and 3 surgeries applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% amitriptyline to his knee, and reported mild to moderate pain relief, without skin irritation nor other side effects.

Example 57A

A 41 year old woman with history of back surgery applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% gabapentin to her back for a period of 2 weeks. She reported mild pain relief.

Example 58

A 53 year old man with a history of two total bilateral knee replacements applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% amitriptyline to both knees for a period of 4 weeks. He reported no pain relief.

Example 58A

A 54 year old man with a history of 7 back surgeries applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% amitriptyline to his back for a period of 2 weeks. He reported mild to moderate pain relief, over and above that he was receiving from a transdermal opiate medication (Duragesic). He reported no side effects, and specifically no skin irritation.

Example 59

A 38 year old man with a history of shoulder strain applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% amitriptyline to his shoulder for a period of 2 weeks. He reported mild to moderate pain relief, and reported no skin irritation nor other side effects.

Example 61

Sufficient carbamazepine and gabapentin was added to a combination of soya lecithin and pluronic to yield a lecithin organogel out 4% a carbamazepine 5% gabapentin.

Example 62

A 42 year old woman with a history of 3 back surgeries and cervical degenerative disc disease applied a mixture, prepared according to example 61, containing 4% carbamazepine and 5% gabapentin to her neck and reported total relief of pain. She reported no side effects, and no skin irritation. She noted the complete and rapid resolution of a migraine like headache at the same time. Administration of

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the same mixture to her arm and her wrist, affected by a diagnosed condition of reflex sympathetic dystrophy, yielded moderate pain relief.

Example 63

3.6 grams gabapentin was dissolved with 5.4 ml ethoxy diglycol using a mortar and pestle. 9.6 grams ketoprofen and 2.7 grams piroxicam were added and the resultant composition mixed well. 19.8 milliliters soya lecithin was added and resultant mixture mixed well and added to a sufficient quantity of 20% pluronic gel to yield 90 milliliters of a composition having about 10 percent ketoprofen, 4% gabapentin and 3% piroxicam.

Example 64

3.6 grams gabapentin was dissolved with 5.4 ml ethoxy diglycol using a mortar and pestle. 9 grams ketoprofen and 0.9 grams piroxicam were added and mixed well. 19.8 milliliters soya lecithin was added to the resultant mixture and mixed well. Sufficient amount of pluronic gel 20% was added to yield 90 milliliters of a composition having approximately 10% ketoprofen, 4% gabapentin and 1% piroxicam.

Example 65

12 g doxepin was mixed with 50 ml Pluronic F 127 33% and placed in a refrigerator to dissolve. 12 g gabapentin was dissolved in 9 ml ethoxy diglycol and mixed to form a smooth paste. 52.8 ml of soya lecithin was added and mixed well. The doxepin/Pluronic mixture was added and mixed well. Sufficient quantity of Pluronic F 127 20% was added to produce 240 ml of a composition having about 5 wt % gabapentin and 5 wt % doxepin.

Example 66

A 36 year old man with a knee injury involving joint surface damage and vascular compromise applied a mixture, prepared generally according to Example 65 to his knee several times per day. He reported moderate to major (40%) relief of pain that persisted for 4 to 6 hours. An earlier trial of carbamazepine-amitriptyline gel produced no relief when applied to his knee.

Example 67

6 gm doxepin was mixed with 18 ml of Pluronic 33% to and placed in a refrigerator to dissolve. 6 gm gabapentin was ground in a mortar and pestle to a fine powder, added to 6 ml ethoxy diglycol and mixed to form a smooth paste. 12 gm guaifenesin was added and mixed well. 26.4 ml soya lecithin was added and mixed well. The doxepin/Pluronic mixture was added and mixed well. Sufficient quantity of Pluronic gel (25.2 ml of 33% Pluronic, although 30% or 20% Pluronic can be used), was added to produce 120 ml of a composition having about 5 wt % gabapentin, about 5 wt % doxepin and about 10 wt % guaifenesin.

Example 68

A 55 year old woman with a back and shoulder injury sustained as a nursing care provider applied a mixture, prepared generally according to Example 67, to her back three times per day for a period of two weeks and achieved major relief. She applied the same mixture to her hip and leg and reported moderate to major relief. A mixture containing only doxepin provided only moderate relief to her back, and

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mild to moderate relief to her hip and leg. A mixture that contained only ketoprofen, gabapentin and piroxicam provided only mild relief to her back.

Example 69

A 59 year old woman with cervical and back strain applied a mixture, prepared generally according to example 51, but without steps involving ketoprofen) containing about 5 wt % doxepin and about 10 wt % guaifenesin, to her neck for a period of two weeks, two to four times per day, and achieved total relief. She applied the same mixture to her back and achieved major to total relief.

Example 70

4.5 gm of doxepin HCl was dissolved using 2.5 ml 95% alcohol and mixed well between syringes. It is also possible to mix the doxepin with 5 ml Pluronic 20% and place in a refrigerator to dissolve. Sufficient quantity of 20% Pluronic F127 was added to produce 90 ml of a composition having about 5 wt % doxepin. Preferably this and other disclosed compositions are protected from light.

Example 71

A 61 year old man with injuries to his back, neck and arm applied a mixture (prepared generally according to Example 70) to his neck four times per day and achieved major relief. He applied the same mixture to his elbow and achieved moderate relief.

Example 72

A formulation of 7% antidepressant and about 10% muscle relaxant was prepared by dissolving 3.15 g of trimipramine and 4.5 g of guaifenesin in a mixer jar using 2.7 mL of ethoxy diglycol. About 9.9 mL of soya lecithin was added and the mixture was mixed well. Sufficient quantity of Pluronic F127 NF (20%) to make total volume of about 45 mL was added and mixed well.

Example 73

A gel formulation of 30% NTHE was prepared from 36 g of celecoxib, 7.2 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (20%) to make total volume of 120 mL.

Example 74

A gel formulation containing about 7% antidepressant and about 13% muscle relaxant was prepared from 14.4 g of doxepin, 31.2 g of guaifenesin, 12 mL of ethoxy diglycol, 52.8 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 240 mL.

Example 75

A gel formulation containing 5% antiepileptic was prepared from 6 g of lamotrigine, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 76

A gel formulation containing 10% adrenergic agonist was prepared from 12 g of crushed tizanidine, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 77

A gel formulation containing 10% muscle relaxant was prepared from 12 g of crushed metaxalone, 6 mL of ethoxy

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diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 78

A gel formulation containing 10% muscle relaxant was prepared from 12 g of crushed carisoprodol, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F 127 NF (33%) to make total volume of 120 mL.

Example 79

A gel formulation containing 10% methocarbamol was prepared from 12 g of crushed methocarbamol, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 80

A gel formulation containing 10% muscle relaxant was prepared from 12 g of crushed dantrolene sodium, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 81A

A gel formulation containing 7% antidepressant, 10% muscle relaxant was prepared from 8.4 g of crushed doxepin, 12 g of chlorzoxazone, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 82

A series of experiments in human subjects were performed using various combinations of pharmaceuticals. The results are indicated in FIG. 2.

Values of pain relief as rated by the patients are provided for each body part for which the medication was administered. The scale used in FIG. 2, is as follows:

0 - None	no benefit or equivalent benefit
1 - Mild	less than 15% pain reduction
1.5 - Mild-moderate	15-33% pain reduction
2.0 - Moderate	25-25% pain reduction
2.5 - Moderate-major	33-45% pain reduction
3.0 - Major	45-60% pain reduction
3.5 - Major-total	60-80% pain reduction
4.0 - Total	greater than 80% pain reduction

For each body part and for each percentage composition of each compounded medication, the individual ratings as well as a mean, which is the statistical mean of the values given according to the scale listed above, are provided. For example, 3 patients were administered doxepin 5% to their back, and the mean level of relief was 2.333. By contrast, 13 patients received the 5%/10% doxepin-guaifenesin combination, and their mean level of pain relief was 2.885. Results for 7/10 and 10/10 compositions of doxepin guaifenesin are also given, and the mean for the entire sample of dox-guai in all combinations is provided at the end of the section, namely 2.722.

The abbreviations used in FIG. 2 are as follows:

Abbreviations	Generic Pharmaceutical names
c-dox-gu	carbamazepine doxepin guaifenesin
c-gab-do	carbamazepine gabapentin doxepin
carb	carbamazepine
carb-ami	carbamazepine amitriptyline
carb-gab	carbamazepine gabapentin
dox	doxepin
dox-chl	doxepin chlorzoxazone
dox-guai	doxepin guaifenesin
g-dox-gu	gabapentin doxepin guaifenesin
gab-dox	gabapentin doxepin
k-ca-dox	ketoprofen carbamazepine doxepin
k-car-pi	ketoprofen carbamazepine piroxicam
k-dox-ch	ketoprofen doxepin chlorzoxazone
k-dox-gu	ketoprofen doxepin guaifenesin
k-dox-pi	ketoprofen doxepin piroxicam
k-g-do-g	ketoprofen gabapentin doxepin guaifenesin
k-gab	ketoprofen gabapentin
k-gab-ami	ketoprofen gabapentin amitriptyline
k-gab-do	ketoprofen gabapentin doxepin
k-gab-gu	ketoprofen gabapentin guaifenesin
k-gab-pi	ketoprofen gabapentin piroxicam
k-pi	ketoprofen piroxicam
la-li-gu	lamotrigine lidocaine guaifenesin
lam-chl	lamotrigine chlorzoxazone
n-dox-ch	naproxen doxepin chlorzoxazone
naproxen	naproxen
tri-chl	trimipramine chlorzoxazone

Based on the results described herein, doxepin appears to be an effective pain relief medication when administered transdermally and appears to be substantially free of side effects when administered transdermally as described herein.

Doxepin appears to provide about three times the positive response rate compared to at least some other pharmaceutical agents described herein, regardless of whether such other pharmaceutical agents are administered singly or in combination. Doxepin appears to be substantially more effective than amitriptyline as a pain, e.g., neuropathic pain agent when administered transdermally. This appears to be true regardless of whether doxepin is administered as a single agent or is administered in combination with other pharmaceuticals as described herein.

Carbamazepine appears to provide positive effects as a pain, e.g., neuropathic pain agent, at least in properly selected patients. Carbamazepine appears to cause a rash in at least some patients, requiring its discontinuation.

These side effects appear similar to those that are noted for oral administration of carbamazepine. Gabapentin appears to be free of side effects when administered transdermally. Although some patients appear to derive some benefit from a combination of transdermally administered ketoprofen, gabapentin, and piroxicam, the effect appears to be relatively weak compared to the effect provided by doxepin.

Guaifenesin appears to provide benefit as an adjunctive treatment, of painful spasticity. For the patient population described herein, amitriptyline appeared to offer limited pain relief when administered transdermally. It appears that combining gabapentin with doxepin may offer some additional benefit. The addition of guaifenesin to doxepin may be of particular value when painful spasticity is present.

In view of the above, the invention provides treatment to patients for whom oral delivery is suboptimal, such as patients who experience gastrointestinal or other side effects, patients who experience poor absorption for orally delivered pharmaceuticals and/or patients who benefit from

delivery over an extended period or a relatively rapid delivery or higher rate of increase of plasma levels. The present invention achieves delivery of therapeutic amounts of pharmaceuticals, for at least some patient populations, substantially without skin irritation, gastrointestinal or other side effects associated with orally-delivered pharmaceuticals, especially psychopharmaceuticals, and yields clinical benefits comparable to or greater than those received by patients to whom corresponding pharmaceuticals were administered orally. In view of the above reasons, particularly effective pain medications are those described in examples 65, 67, 69 and 70.

A number of variations and modifications of the invention can also be used. It is believed that blood plasma levels may be increased by providing for two or more transdermal applications per day and/or applying a transdermal composition to two or more sites.

In at least one case, application of a Prozac gel formulation twice daily appeared to approximately double the plasma level. It is believed that an approach such as applying a Prozac gel formulation twice daily to two sites will yield middle range therapeutic levels of about 140-250 ng/ml. At least partially on the basis of the results described herein for fluoxetine, it is believed olanzapine (sold under the trade name Zyprexa) or a fluoxetine/olanzapine mixture in a lecithin organogel will prove useful.

Other types of psychotropic or psychopharmaceutical medications for which the described transdermal delivery may be used including psychostimulant medications. One example of a psychostimulant medication is Methylphenidate (sold under the trade name Ritalin) used in the treatment of attention deficit hyperactivity disorder (ADHD). Methylphenidate typically has a 2-4 hour duration of action necessitating frequent dosing of a patient which is particularly difficult to accomplish with children in school. It is believed that by using transdermal administration, it will be possible to achieve an extension of effective dosing throughout the day, eliminating the need for frequent oral medication administration. It is believed that transdermal administration will also eliminate peaks and valleys of blood plasma levels which, it is believed, will be more clinically effective. It is believed similar results will be obtained with other pharmaceuticals, for example, Dextroamphetamine (under the trade name Dexedrine) although it is believed the need is less acute since a time release "spansule" form of the medication is available which typically has a 5-6 hour duration of action. Another group of psychotropic medications which, it is believed, will benefit from transdermal delivery includes antipsychotic medication such as those used in the treatment in schizophrenia.

Embodiments of the invention include, but are not necessarily limited to, use by patients with enteric absorption deficits.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

What is claimed is:

1. A method for treating pain in a subject comprising contacting said subject with a transdermal composition comprising:

a psychopharmaceutical and guaifenesin in an amount effective to treat pain, and lecithin organogel,

thereby treating pain in said subject.

2. The method of claim 1, wherein said psychopharmaceutical is selected from the group consisting of sertraline,

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fluoxetine, carbamazepine, amitriptyline, trazodone, fluvoxamine, pemoline, pergolide, bromocriptine mesylate, propranolol, bupropion, reboxetine, valproic acid, nefazodone and doxepin.

3. The method of claim 1, wherein said transdermal composition further comprises Pluronic F127.

4. The method of claim 1, wherein said psychopharmaceutical is doxepin.

5. The method of claim 1, wherein said transdermal composition comprises about 5 wt % doxepin.

6. The method of claim 1, wherein said transdermal composition comprises about 10 wt % guaifenesin.

7. The method of claim 1, wherein said transdermal composition comprises about 5 wt % doxepin and about 10 wt % guaifenesin.

8. A method for treating pain in a subject comprising contacting said subject with a transdermal composition comprising:

doxepin and guaifenesin in an amount effective to treat pain, and lecithin organogel,

thereby treating pain in said subject.

9. The method of claim 8, wherein said transdermal composition comprises about 5 wt % doxepin.

10. The method of claim 8, wherein said transdermal composition comprises about 10 wt % guaifenesin.

11. The method of claim 8, wherein said transdermal composition comprises about 5 wt % doxepin and about 10 wt % guaifenesin.

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12. A method for treating pain in a subject comprising contacting said subject with a transdermal composition comprising:

doxepin and guaifenesin in an amount effective to treat pain, Pluronic F127, and lecithin organogel,

thereby treating pain in said subject.

13. The method of claim 12, wherein said transdermal composition comprises about 5 wt % guaifenesin.

14. The method of claim 12, wherein said transdermal composition comprises about 10 wt % guaifenesin.

15. The method of claim 12, wherein said transdermal composition comprises about 5 wt % doxepin and about 10 wt % guaifenesin.

16. A method for treating pain in a subject comprising contacting said subject with a transdermal composition comprising:

about 5 wt % doxepin, about 10 wt % guaifenesin, and lecithin organogel,

thereby treating pain in said subject.

17. A method for treating pain in a subject comprising contacting said subject with a transdermal composition comprising:

about 5 wt % doxepin, about 10 wt % guaifenesin, Pluronic F127, and lecithin organogel,

thereby treating pain in said subject.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

ENT NO. : 6,479,074 B2
ED : November 12, 2002
INVENTOR(S) : Robert W. Murdock et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 36,

Line 8, delete the word "guaifenesin" and replace it with the word -- doxepin --

Signed and Sealed this

Thirteenth Day of May, 2003

A handwritten signature in black ink, appearing to read "James E. Rogan", with a horizontal line drawn underneath it.

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

(12) **United States Patent**
Murdock et al.

(10) Patent No.: **US 6,572,880 B2**
 (45) Date of Patent: **Jun. 3, 2003**

(54) **METHODS AND TRANSDERMAL
 COMPOSITIONS FOR PAIN RELIEF**

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(*) Notice: Subject to any disclaimer, the term of this
 patent is extended or adjusted under 35
 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 09/754,500

(22) Filed: Jan. 3, 2001

(65) Prior Publication Data

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Related U.S. Application Data

(63) Continuation-in-part of application No. 09/342,679, filed on
 Jun. 29, 1999, now abandoned, which is a continuation-in-
 part of application No. 09/106,684, filed on Jun. 29, 1998,
 now Pat. No. 6,290,986, which is a continuation-in-part of
 application No. 08/957,485, filed on Oct. 24, 1997, now
 abandoned

(60) Provisional application No. 60/029,120, filed on Oct. 24,
 1996, and provisional application No. 60/122,903, filed on
 Mar. 5, 1999.

(51) Int. Cl.⁷ A61F 13/02; A61L 15/16

(52) U.S. Cl. 424/449; 424/448

(58) Field of Search 424/448, 449

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 Giulio A DeConti, Jr.; Maria Laccotripe Zacharakis

(57) **ABSTRACT**

The present invention features methods and compositions
 for transdermal administration. In one embodiment, the
 invention features methods and compositions for transder-
 mal administration of an amine containing compound hav-
 ing biphasic solubility and/or an agent which enhances the
 activity of the amine containing compound having biphasic
 solubility, e.g., a muscle relaxant, to relieve pain.

1 Claim, 11 Drawing Sheets

cpt 90862 Medication Management (cdw ver. 4-24-95)

90862.DOC

Patient: _____ Date _____

Current Medication: 1) _____
2) _____
3) _____
4) _____
5) _____
6) _____

Diagnoses: Axis 1: _____
Axis 2: _____ Axis 3: _____
GAF _____

Subjective: _____

Objective :	APPEARANCE _____	AFFECT _____
	SPEECH _____	CONCENTRATION _____
	MEMORY _____	IRRITABILITY _____
	APPETITE _____	AV HALLUC. _____
	CRYING SPELLS _____	ENERGY LEVEL _____
	SLEEP _____	WEIGHT _____

SIDE EFFECTS: _____

RESPONSE OF DEPRESSION SYMPTOMS TO MEDICATIONS:

EXCELLENT	GOOD	FAIR	POOR	N/A
-----------	------	------	------	-----

RESPONSE OF ANXIETY SYMPTOMS TO MEDICATIONS:

EXCELLENT	GOOD	FAIR	POOR	N/A
-----------	------	------	------	-----

CONCURRENT MEDICATION CONDITIONS: _____

ASSESSMENT: _____

PLAN: 1) Continue meds: _____
2) Change dosage: _____
3) New Med: _____
4) _____

LAB STUDIES ORDERED: _____
OTHER: _____

Fig. 1

Case Processing Summary(a)

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
ankle * MEDS * Composition	4	3.1%	127	96.9%	131	100.0%
arm * MEDS * Composition	10	7.6%	121	92.4%	131	100.0%
Back * MEDS * Composition	69	52.7%	62	47.3%	131	100.0%
elbow * MEDS * Composition	11	8.4%	120	91.6%	131	100.0%
headache * MEDS * Composition	131	100.0%	0	.0%	131	100.0%
Knee * MEDS * Composition	19	14.5%	112	85.5%	131	100.0%
hip * MEDS * Composition	15	11.5%	116	88.5%	131	100.0%
Neck * MEDS * Composition	28	21.4%	103	78.6%	131	100.0%
leg * MEDS * Composition	13	9.9%	118	90.1%	131	100.0%
shoulder * MEDS * Composition	25	19.1%	106	80.9%	131	100.0%
wrist * MEDS * Composition	26	19.8%	105	80.2%	131	100.0%
a Limited to first 150 cases						

P

					Case Number	ankle	arm
	c-dox-gu	Composition	5/5/10	1	26	.	.
				2	33	.	.
				3	41	.	.
				4	59	.	.
				5	73	.	.
				6	80	.	.
			4/5/10	Total	N		
					Mean		
				1	98	.	.
				2	112	.	.
				Total	N		
					Mean		

Fig. 2A

		Total	N				
			Mean				
c-gab-do	Composition	5/5/5	1		34	.	.
			Total	N			
		Total	Mean				
			N				
carb	Composition	4	1		5	.	.
			Total	N			
		6	Mean				
			1		81	.	.
		Total	Total	N			
			Mean				
		Total	N				
			Mean				
carb-ami	Composition	4/5	1		12	.	.
			2		40	.	.
			3		49	.	.
			4		64	.	.
		Total	Total	N			
			Mean				
		Total	N				
			Mean				
carb-gab	Composition	4/4	1		27	.	mild-moderate
			2		35	.	.
			3		126	.	moderate
		Total	Total	N			2
			Mean				1.750
		Total	N				2
			Mean				1.750
			1		4	.	moderate
			2		13	.	.
			3		15	.	.

Fig. 2B

dox	Composition	5	4	42	.	.
			5	46	.	none
			6	74	.	.
			7	95	moderate	.
			8	116	.	.
			9	121	.	.
			10	128	.	moderate
			Total	N	1	3
				Mean	2.000	1.333
			Total	N	1	3
				Mean	2.000	1.333
	Composition	7/13	1	10	.	.
			Total	N		
				Mean		
		5/10	1	21	.	.
			2	29	.	.
			3	30	.	.
			Total	N		
				Mean		
		7/10	1	83	.	.
			Total	N		
				Mean		
		Total	N			
			Mean			
			1	7	.	.
			2	9	.	.
			3	14	.	.
			4	18	.	.
			5	20	.	.
			6	25	.	.
			7	36	.	.
			8	50	.	.

Fig. 2C

dox-guai	Compsition	5/10	9	58	.	.
			10	71	.	.
			11	76	.	.
			12	77	.	.
			13	90	.	.
			14	97	.	.
			15	101	.	.
			16	103	.	.
			17	108	.	.
			18	123	.	.
			19	131	.	.
			Total	N		
				Mean		
		7/10	1	22	.	.
			2	47	.	.
			3	111	.	.
			Total	N		
				Mean		
		10/10	1	23	.	.
			2	48	.	.
			3	53	.	.
			4	57	.	.
			5	67	.	.
			Total	N		
				Mean		
		Total	N			
			Mean			
		4/5/10	1	11	.	.
			Total	N		
				Mean		
			1	1	.	.
			2	32	.	.
			3	39	.	.

Fig. 2D

MEDS	g-dox-gu	Composition	5/5/10	4	44	.	.
				5	51	.	.
				6	54	.	.
				7	62	.	.
				8	72	.	.
				9	85	.	.
				10	87	.	.
				11	93	.	.
				12	119	.	.
				13	129	.	.
				Total	N		
					Mean		
				Total	N		
					Mean		
	gab-dox	Composition	5/5	1	37	.	.
				2	65	.	.
				3	68	.	.
				Total	N		
					Mean		
				Total	N		
					Mean		
	k-ca-dox	Composition	10/4/5	1	86	.	.
				Total	N		
					Mean		
				Total	N		
					Mean		
			10/6/3	1	43	.	.
				Total	N		
					Mean		
				1	102	.	.

Fig. 2E

k-car-pi	Composition	10/4/3	2		104	.	.
			Total	N			
				Mean			
		Total	N				
k-dox-ch	Composition	20/10/5	1		100	.	.
			Total	N			
				Mean			
		Total	N				
k-dox-gu	Composition	3/5/5	1		6	.	.
			Total	N			
		20/5/10	1		63	.	.
			Total	N			
				Mean			
		Total	N				
k-dox-pi	Composition	10/4/3/5	1		122	.	.
			Total	N			
				Mean			
		Total	N				
			Mean				
			k-g-do-g	Composition	10/4/5/10	1	
Total	N						
	Mean						
Total	N						
k-gab	Composition	20/4	1		115	.	none
			Total	N			1
				Mean			.000
		Total	N				1
			Mean				.000
			1		117	.	.

k-gab-am	Composition	20/5/5	Total	N			
				Mean			
k-gab-do	Composition	Total	N				
			Mean				
		20/4/5	1		55	.	.
			Total	N			
		10/5/4					
			Total	N			
		10/5/5	1		99	major	.
			Total	N		1	
		20/5/5				3.000	
			Total	N			
		20/5/5	1		113	.	.
			Total	N			
		Total					
			Mean				
k-gab-gu	Composition	20/4/4/1	1		94	.	.
			Total	N			
		20/5/5					
			Total	N			
		Total	1		105	.	.
			Total	N			
			Mean				
			1		2	.	.
			2		8	major	.
			3		19	.	.
			4		31	.	.
			5		38	.	.
			6		45	none	.

Fig. 2G

k-gab-pi	Composition	10/4/3	7	56	.	.
			8	78	.	.
			9	89	.	.
			10	109	.	.
			11	120	.	.
			12	124	.	.
			13	130	.	.
			Total	N		2
				Mean		1.500
		10/4/1	1	16	.	.
			2	28	.	mild
			3	52	.	.
			4	66	.	.
			5	69	.	.
			6	75	moderate	.
			7	82	.	.
			8	84	.	.
			9	88	.	.
			10	91	.	.
			11	96	major	.
			12	125	.	.
			Total	N	2	1
				Mean	2.500	1.000
		10/1/3	1	114	.	.
			Total	N		
		Total	N		2	3
			Mean		2.500	1.333
k-pi	Composition	10/3	1	127	.	.
			Total	N		
		Total	Mean			
			1	110	.	.

Fig. 2H

la-li-gu	Composition	5/5/10	Total	N			
		Total	Mean				
lam-chl	Composition	7/10	1		3	.	moderate-major
			Total	N			1
			Mean				2.500
		10/10	1		24	.	.
			2		70	.	.
			3		106	.	.
			Total	N			
			Mean				
		Total	N				1
			Mean				2.500
n-dox-ch	Composition	30/5/5	1		79	.	.
			Total	N			
			Mean				
		Total	N				
naproxen	Composition	30	1		60	.	.
			Total	N			
		Total	N				
tri-chl	Composition	7/10	1		61	.	.
			Total	N			
			Mean				
		7/13	1		92	.	.
			2		107	.	.
			Total	N			
			Mean				
		Total	N				
			Mean				

Fig. 2I

	Total	N		4	10
		Mean		2.500	1.400
June 2 1999 N=131					
a Limited to first 150 cases					

Fig. 2J

METHODS AND TRANSDERMAL COMPOSITIONS FOR PAIN RELIEF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 09/342,679 filed on Jun. 29, 1999 now abandoned, which in turn, is a continuation-in-part of U.S. patent application Ser. No. 09/106,684 filed on Jun. 29, 1998 now issued as U.S. Pat. No. 6,290,986 B1, which in turn is a continuation-in-part of U.S. patent application Ser. No. 08/957,485 filed on Oct. 24, 1997 now abandoned. This application also claims priority to PCT Application Serial No. PCT/US99/14653 filed on Jun. 29, 1999, U.S. Provisional Patent Application No. 60/122,903 filed on Mar. 5, 1999, PCT Application Serial No. PCT/US97/19651 filed on Oct. 24, 1997, and U.S. Provisional Patent Application Serial No. 60/029,120 filed on Oct. 24, 1996. The contents of each of the foregoing applications are incorporated herein in their entirety by this reference.

FIELD OF THE INVENTION

The present invention is directed to methods and compositions for transdermal administration. In particular, the present invention is directed to methods and compositions for the transdermal administration of an amine containing compound having biphasic solubility and/or an agent which enhances the activity of the amine containing compound having biphasic solubility, e.g., a muscle relaxant, to relieve pain.

BACKGROUND OF THE INVENTION

It is believed that damage to somatic sensory nerves causes a somatic sensory loss. Such damage can be caused by a variety of means including trauma, diseases such as diabetes, herpes zoster and late-stage cancer, chemotherapy, or by a chemical injury. It is believed that neural pain circuits rewire themselves, both anatomically and biochemically, after nerve injury. In many patients suffering from damage to somatic sensory nerves, negative symptoms such as numbness are joined by positive sensations, involving a sort of false sensation of pain. The experience can range from mild dysesthesia to excruciating pain, rendering some patients unable to work, walk or do other daily activities.

In the past, patients were generally treated by administration of analgesics to relieve pain. A vast majority of such patients receive doses of these agents orally. Unfortunately, in some situations, oral administration of such agents has been associated with a variety of side effects, such as liver damage, kidney damage, gastrointestinal side effects, addiction, sedation, and/or weight gain which cannot be tolerated well by the patient. In other cases, malabsorption of oral preparations have resulted in subtherapeutic plasma levels. In other cases, the agents have relatively short plasma half-lives, necessitating inconveniently frequent dosing. In general, oral delivery involves a time delay as the analgesic is absorbed via the digestive system before entering the bloodstream. A number of agents which have traditionally been administered orally or by injection have been inappropriate or suboptimal for some patients when so-administered. There are a number of medications which, in at least some patients, are not tolerated well when orally administered (e.g. which cause undesirable gastrointestinal or other side effects) and/or which provide undesirably high or low concentrations or delayed concentrations in a target tissue. In some cases, dosages which are appropriate for oral

administration, upon being distributed more or less uniformly throughout the body, are undesirably low in a particular area, e.g., tissue, to achieve desired results. Oral or injection administration may result in too slow or too rapid increase in blood plasma levels, e.g., may involve an undesirably long time delay as the analgesic is absorbed by the digestive system before entering the bloodstream, or may result in a "spike" in blood plasma levels followed by an undesirably low level, where a more constant level would be preferable. Some analgesics are particularly prone to cause or contribute to kidney or liver damage when administered orally.

Although other forms of delivery of pharmaceuticals agents are known, each has its drawbacks. Parenteral (i.e., intravenously or intramuscularly injected) administration is inconvenient and expensive, and is rarely used outside the hospital. Inhalation is believed to be not feasible with many analgesic agents currently in use. Therefore, there is a need for an analgesic delivery system which provides effective and acceptable levels, while preferably avoiding or reducing undesired effects such as liver damage or gastrointestinal side effects.

SUMMARY OF THE INVENTION

The present invention provides a transdermal composition for the treatment of pain in a subject, particularly a human subject. The transdermal composition for the treatment of pain in a subject includes an amine containing compound having biphasic solubility in an amount effective to treat pain in a subject and a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound, e.g., a lecithin organogel carrier. In a preferred embodiment, the transdermal composition further includes an agent which enhances the activity of the amine containing compound having biphasic solubility, e.g., a muscle relaxant, such as guaifenesin, chlorzoxazone, dantrolene sodium, metaxalone, carisoprodol, and combinations thereof. Preferably, the agent which enhances the activity of the amine containing compound having biphasic solubility, e.g., the muscle relaxant, also has a biphasic solubility.

In one embodiment of the present invention, the amine containing compound having biphasic solubility is an antidepressant compound, such as a tricyclic antidepressant compound, e.g., doxepin or trimipramine.

In another embodiment of the present invention, the amine containing compound having biphasic solubility is a sodium channel blocker, a calcium channel blocker, an anti-epileptic compound, or an anti-convulsant compound.

Another embodiment of the invention features a transdermal composition which includes an amine-containing compound as described herein and an anti-inflammatory compound, such as a nonsteroidal anti-inflammatory compound, e.g., celecoxib, etodolac, mefenamic acid, nabumetone, salsalate, naproxen, vioxx®, and combinations thereof. Such a composition can further include an agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant such as guaifenesin.

In another aspect, the invention features a transdermal composition for the treatment of pain in a subject including an amine containing compound having biphasic solubility in an amount effective to treat pain in a subject; a muscle relaxant in an amount effective to enhance the activity of the amine containing compound having biphasic solubility; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound having biphasic solubility and the muscle relaxant.

In yet another aspect, the invention features a transdermal composition for the treatment of pain in a subject including doxepin in an amount effective to treat pain in a subject; guaifenesin in an amount effective to enhance the activity of doxepin; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the doxepin and the guaifenesin.

Other aspects of the invention feature methods for treating pain in a subject in which the subject is contacted with a transdermal composition including an amine containing compound having biphasic solubility in an amount effective to treat pain in the subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound to thereby treat pain in the subject. In a preferred embodiment, the transdermal composition is applied to the skin of the subject.

Another aspect of the invention features a method for selecting a compound suitable for treating pain in a subject. The method includes transdermally administering an amine containing compound having biphasic solubility to a subject; and determining whether pain is treated in the subject to thereby select a compound suitable for treating pain in a subject. In a preferred embodiment, the method can further include modeling the compound using a computer equipped with a three-dimensional chemical structure modeling program; and determining whether the three-dimensional chemical structure of the compound possesses sufficient characteristics to be useful as a sodium channel blocker or a calcium channel blocker, thereby selecting a compound suitable for treating pain in a subject.

In another aspect, the invention features a transdermal composition suitable for transdermal delivery, which includes a therapeutically effective amount of a pharmaceutical compound (e.g., a serotonin specific reuptake inhibitor, a mood stabilizing compound, a dopamine compound, a compound suitable for treating attention deficit hyperactivity disorder, a compound suitable for treating hypertension and akathisia, an analgesic compound, or a compound used in the treatment of impotence) and a pharmaceutically acceptable carrier suitable for transdermal delivery of the pharmaceutical compound, e.g., a lecithin organogel carrier.

In yet another aspect, the invention features a transdermal composition for treatment of pain in a subject which includes a compound capable of blocking afferent neuron transmission in an amount effective to block afferent neuron transmission in a subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the compound.

In a further aspect, the present invention features transdermal compositions comprising lamotrigine and doxepin; topiramate and chlorzoxazone; topiramate and guaifenesin; topiramate and doxepin; topiramate and naproxen; doxepin and chlorzoxazone; lamotrigine and guaifenesin; lamotrigine, doxepin, and guaifenesin; or lamotrigine, doxepin, and chlorzoxazone.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is an evaluation form used in evaluating an embodiment of the present invention.

FIG. 2 is a table depicting the results from clinical experiments using compositions of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a transdermal composition suitable for treatment of pain in a subject. The transdermal

composition includes an amine containing compound having biphasic solubility in an amount effective to treat pain in a subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound having biphasic solubility.

As used herein, the term "subject" includes a mammal, such as a human, a horse, a pig, a cow, a mouse, a rat, a rabbit, or a goat. In preferred embodiment, the subject is a human.

As used herein, the term "pain" is art recognized and includes a bodily sensation elicited by noxious chemical, mechanical, or thermal stimuli, in a subject, e.g., a mammal such as a human. The term "pain" includes chronic pain, such as lower back pain; pain due to arthritis, e.g., osteoarthritis; joint pain, e.g., knee pain or carpal tunnel syndrome; myofascial pain, and neuropathic pain. The term "pain" further includes acute pain, such as pain associated with muscle strains and sprains; tooth pain; headaches; pain associated with surgery; or pain associated with various forms of tissue injury, e.g., inflammation, infection, and ischemia.

As used herein, the term "amine containing compound having biphasic solubility" includes compounds having at least one amine moiety and having sufficient lipid solubility (e.g., solubility in polar solvents such as ethanol, ethoxydiglycerol, ethoxydiglycol, chloroform, benzene, and the like) such that the compound passes through the stratum corneum, and has sufficient aqueous solubility to be active in the aqueous environment of the dermis and the underlying tissue.

Transdermal compositions of the present invention include an amine containing compound having biphasic solubility in an amount effective to treat pain in a subject. As used herein, the terms "amount effective to treat pain in a subject" and "effective amount" are used interchangeably herein and include an amount effective, at dosages and for periods of time necessary, to achieve the desired result, e.g., sufficient to treat pain in a subject. An effective amount of an amine containing compound or a pharmaceutical compound as defined herein may vary according to factors such as the disease state, age, and weight of the subject, and the ability of the amine containing compound or pharmaceutical compound to elicit a desired response in the subject. Dosage regimens may be adjusted to provide the optimum therapeutic response. An effective amount is also one in which any toxic or detrimental effects of the amine containing compound having biphasic solubility or pharmaceutical compound are outweighed by the therapeutically beneficial effects.

The transdermal compositions of the invention can further include an agent which enhances the activity of the amine containing compound having biphasic solubility. As used herein, an "agent which enhances the activity of the amine containing compound having biphasic solubility" includes an agent which enhances the pharmacological activity of the amine containing compound having biphasic solubility (e.g., the ability of the amine containing compound to treat pain), or enhances the transdermal delivery of the amine containing compound having biphasic solubility (e.g., the ability of the amine containing compound to cross the stratum corneum), or enhances both the pharmacological activity and the transdermal delivery of the amine containing compound. Examples of agents which enhance the activity of the amine containing compound having biphasic solubility, include muscle relaxants, described in further detail below.

As used herein, the term "transdermal" composition includes compositions capable of passing through the stra-

tum corneum of a subject. The term transdermal further includes compositions capable of passing through the epidermis of a subject, compositions capable of passing through the dermis of a subject, and compositions capable of passing through the hypodermis of a subject. In preferred embodiments, the term transdermal includes compositions capable of passing through the skin of a subject and reaching the underlying tissues and organs.

As used herein, the term "transdermal delivery" includes delivery of, for example, a compound through the stratum corneum of a subject. The term transdermal delivery further includes delivery of, for example, a compound through the epidermis of a subject, delivery of, for example, a compound through the dermis of a subject, and delivery of, for example, a compound through the hypodermis of a subject. In preferred embodiments, the term transdermal delivery includes delivery of, for example, a compound through the skin of a subject to the underlying tissues and organs.

The present invention further features a transdermal composition for treatment of pain in a subject which includes a compound capable of blocking afferent neuron transmission in an amount effective to block afferent neuron transmission in a subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the compound.

As used herein, the term "compound capable of blocking afferent neuron transmission" includes a compound which is capable of blocking the ability of an afferent neuron, i.e., a sensory neuron, to carry an impulse toward the central nervous system.

Various aspects of the invention are described in further detail in the following subsections:

Amine Containing Compounds Having Biphasic Solubility

Amine containing compounds having biphasic solubility for use in the transdermal compositions of the invention include antidepressant compounds, antiepileptic compounds, anticonvulsant compounds, sodium channel blockers and calcium channel blockers.

As used herein, the term "antidepressant compounds" includes compounds capable of alleviating the symptoms of depression. Examples of antidepressant compounds include all tricyclic antidepressants (e.g., amitriptyline, dothiepin, or lofepramine), bupropion (sold under the trade name Wellbutrin), reboxetine (sold under the trade name Edronax), nefazodone (sold under the trade name Serzone) and trazodone (sold under the trade name Desyrel). Antidepressant compounds are described in, for example, the 1998 SIGMA catalogue and the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, the contents of which are incorporated herein by reference.

In one embodiment of the present invention, the antidepressant compounds of the present invention contain a tricyclic moiety. Therefore, in a preferred embodiment, a transdermal composition of the present invention includes a tricyclic antidepressant compounds. Exemplary tricyclic antidepressants include adinazolam, amitriptylinoxide, amoxapine, clomipramine, demexiptiline, dimetacrine, dothiepin, doxepin, imipramine N-oxide, iprindole, lofepramine, melitracen, metapramine, noxiptilin, pizotiline, propizepine, quinupramine, tianeptine, and trimipramine. A particularly preferred tricyclic antidepressant for use in the compositions of the invention is doxepin.

Tricyclic antidepressant compounds are described in, for example, "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995), the contents of which are incorporated herein by reference.

Preferably, the tricyclic antidepressant compound is selected from the group consisting of doxepin, trimipramine,

other tricyclics having biphasic solubility, and combinations thereof. When combined with other compounds, such as an agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant, and/or an anti-inflammatory compound, e.g., a nonsteroidal anti-inflammatory compound, as discussed below, the tricyclic antidepressant preferably constitutes from about 1% by weight (% by wt.) to about 30% by wt. of the total amount of the pharmaceutical, more preferably from about 3% by wt. to about 15% by wt., and most preferably from about 5% by wt. to about 13% by wt.

The amine containing compounds having biphasic solubility used in the transdermal compositions of the invention further include antiepileptic compounds. As used herein, the term "antiepileptic compound" includes compounds capable of alleviating the symptoms of epilepsy. Exemplary antiepileptic compounds for use in the compounds of the invention include lamotrigine, felbamate, and carbamazepine. Preferably, the antiepileptic compound is selected from the group consisting of lamotrigine, felbamate, carbamazepine, and combinations thereof. When combined with other compounds, such as an agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant, and/or an anti-inflammatory compound, e.g., a nonsteroidal anti-inflammatory compound as discussed below, the antiepileptic compound constitutes from about 1% by wt. to about 30% by wt. of the total amount of the pharmaceutical, more preferably from about 3% by wt. to about 20% by wt., and most preferably from about 5% by wt. to about 15% by wt. Antiepileptic compounds are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, and the "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995) the contents of which are incorporated herein by reference.

In another aspect of the present invention, the amine containing compounds having biphasic solubility of the present invention include anticonvulsant compounds. As used herein, the term "anticonvulsant compound" includes compounds capable of alleviating the symptoms of convulsion, i.e., the violent involuntary tetanic contractions of an entire group of muscles. Exemplary anticonvulsant compounds which for use in the compositions of the invention include felbamate, lamotrigine and carbamazepine. Preferably, the anticonvulsant compound is selected from the group consisting of felbamate, lamotrigine, and combinations thereof. When combined with other compounds, such as an agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant, and/or an anti-inflammatory compound, e.g., a nonsteroidal anti-inflammatory compound as discussed below, the anticonvulsant compound constitutes from about 1% by wt. to about 30% by wt. of the total amount of the pharmaceutical, more preferably from about 3% by wt. to about 20% by wt., and most preferably from about 5% by wt. to about 15% by wt. Anticonvulsant compounds are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, and the "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995) the contents of which are incorporated herein by reference.

In yet another aspect of the present invention, the amine containing compounds having biphasic solubility of the present invention include adrenergic agonist compounds. Preferably, the adrenergic agonist compound is tizanidine. When combined with other compounds, such as a muscle relaxant and/or nonsteroidal anti-inflammatory compound as

discussed below, the adrenergic agonist compound constitutes from about 1% by wt. to about 30% by wt. of the total amount of the pharmaceutical, more preferably from about 3% by wt. to about 20% by wt., and most preferably from about 5% by wt. to about 15% by wt. Adrenergic agonist compounds are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, and the "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995) the contents of which are incorporated herein by reference.

The amine containing compounds having biphasic solubility used in the transdermal compositions of the invention further include sodium channel blockers and calcium channel blockers. As used herein, the term "sodium channel blockers" includes compounds which are capable of blocking the activity of a sodium channel. Examples of sodium channel blockers include topiramate, tetrodotoxin, flecainide, disopyramide, and terfenadine. Sodium channel blockers are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, and the "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995) the contents of which are incorporated herein by reference. As used herein, the term "calcium channel blockers" includes compounds which are capable of blocking the activity of a calcium channel. Examples of calcium channel blockers include Arylalkylamines, e.g., Bepridil, Clentiazem, Diltiazem, Fendiline, Gallopamil, Mibefradil, Prenylamine, Semotiadil, Terodiline, or Verapamil; Dihydropyridine Derivatives, e.g., Amlodipine, Aranidipine, Barnidipine, Benidipine, Cilnidipine, Bfonidipine, Elgodipine, Felodipine, Isradipine, Lacidipine, Lercanidipine, Manidipine, Nicardipine, Nifedipine, Nilvadipine, Nimodipine, Nisoldipine, or Nirrendipine; Piperazine Derivatives, e.g., Cinnarizine, Flunarizine, Lidoflazine, or Lomerizine; Bencyclane; Etafenone; Fantofarone; or Perhexiline.

Whenever nerves are damaged, for example, by trauma, by diseases such as diabetes, herpes zoster, or late-stage cancer, or by chemical injury (e.g., as an untoward consequence of agents including the false-nucleoside anti-HIV pharmaceuticals), neural pain circuits rewire themselves, anatomically and/or biochemically. Thus, following an injury, new sodium and calcium channels are formed which are believed to constitute the basis for chronic pain development. Through a similar action in the dorsal root ganglia, chronic regional pain syndromes may develop. Each time one of these sodium and/or calcium channels depolarizes, a nerve impulse originates. Because there are so many sodium and calcium channels, there may be a constant cascade of nerve impulses, causing allodynia, burning sensations, and/or dysesthesias. It is believed that some chronic pains may be mediated through sodium and/or calcium channels in nerve cells. Thus, it is believed that amine containing compounds having biphasic solubility which can block sodium and/or calcium channels may also be used in the transdermal compositions of the invention.

In one embodiment of the invention, the amine moiety of the amine containing compounds having biphasic solubility of the present invention may function similar to a sodium or calcium ion upon entry into the sodium channel of a nerve cell membrane. A non-polar moiety, which is preferably present in the amine containing compound having biphasic solubility of the present invention may interact with the nerve cell membrane, perhaps through Van der Waals forces. In such cases, it is believed that the presence of the non-polar

moiety prevents or inhibits a complete uptake of the amine containing compound having biphasic solubility through the nerve cell membrane. It is believed that one or more these interactions prevent or reduce the amount and/or the rate of depolarization and ion exchange involved in stimulus conduction, thereby decreasing pain sensation.

The amount of an amine containing compound having biphasic solubility useful in relieving pain transdermally may be determined by methods known in the art, and typically ranges from about 1 mg to about 300 mg per subject per dose, preferably from about 5 mg to about 100 mg per subject per dose, and more preferably from about 10 mg to about 50 mg per subject per dose, depending on a variety of factors including the particular amine containing compound having biphasic solubility used, whether the area of transdermal application is the site of action, and the intended size of the site of action. In a preferred embodiment, the amount of an amine containing compound having biphasic solubility useful in relieving pain transdermally, is 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 mg, 150 mg, 200 mg, 250 mg, or 300 mg per subject per dose.

Muscle Relaxants

Transdermal compositions of the present invention may also include a muscle relaxant. As used herein, the term "muscle relaxant" includes compounds which facilitate or enhance the relaxation of muscles (e.g., provide relief from muscle spasm) and, thus, facilitate or enhance the transdermal delivery of the transdermal compositions of the invention. Exemplary muscle relaxants include both skeletal muscle relaxants and smooth muscle relaxants such as anticholinergics, antispasmodics, bronchodilators, and vasodilators. Muscle relaxants are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, pp. THER-1 to THER-28, and the "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995) the contents of which are incorporated herein by reference. Preferably, the muscle relaxant is selected from the group consisting of guaifenesin, benzodiazepines (e.g., clozapine or diazepam), chlorzoxazone, dantrolene sodium, metaxalone, carisoprodol, other muscle relaxants having biphasic solubility, and combinations thereof. More preferably, the muscle relaxant is selected from the group consisting of guaifenesin, chlorzoxazone, and combinations thereof. A preferred muscle relaxant for use in the compositions of the invention is guaifenesin.

Preferably the muscle relaxant has biphasic solubility. Preferably the muscle relaxant, when present in the pharmaceutical composition, constitutes from about 1% by wt. to about 30% by wt. of the total amount of the pharmaceutical, more preferably from about 3% by wt. to about 20% by wt., and most preferably from about 5% by wt. to about 15% by wt.

Anti-Inflammatory Compounds

The transdermal compositions of the present invention may also include an anti-inflammatory compound. As used herein, the term "anti-inflammatory compound" includes a compound which is capable of reducing cell migration, caused by ischemic and trauma associated events, and therefore reduces edema formation to thereby provide pain relief. Preferably, the anti-inflammatory compound is a nonsteroidal anti-inflammatory compound (i.e., NTHE) including ketoprofen. Anti-inflammatory compounds, e.g., NTHes, are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, pp. THER-1 to

Ther-28, and the "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995) the contents of which are incorporated herein by reference. Preferably, the NTHE is selected from the group consisting of celecoxib, etodolac, mefenamic acid, nabumetone, salsalate, naproxen, Vioxx®, COX-2 NTHEs having biphasic solubility, and combinations thereof.

More preferably, the NTHE is selected from the group consisting of celecoxib, etodolac, naproxen, COX-2 NTHEs having biphasic solubility, and combinations thereof. Preferably, the NTHE has biphasic solubility. The NTHE, when present in the transdermal composition, preferably, constitutes from about 1% by wt. to about 30% by wt. of the total amount of the pharmaceutical, more preferably from about 3% by wt. to about 30% by wt., and most preferably from about 5% by wt. to about 30% by wt.

Dosages

The concentration as well as the quantity of the amine containing compounds having biphasic solubility, the agents which enhance the activity of the amine containing compounds, e.g., the muscle relaxants, and the anti-inflammatory compounds can be varied independently in order to achieve the desired effect. For example, higher concentrations of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds contained in a dosage form of decreased viscosity may result in an analgesic with fast onset and short duration. High concentrations of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds contained in a dosage form of increased viscosity may result in potent analgesic with fast onset and long duration. Low concentrations of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds in a dosage form of decreased viscosity may result in mild analgesic with longer onset and short duration. Low concentrations of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds contained in a dosage form of increased viscosity may have mild analgesic properties with longer onset and longer duration. The ability to vary the concentration of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds from very low to high of the total composition, combined with the ability to coat thin (about 0.1 mm) or thick (about 0.5 mm) enables the practitioner of the invention to vary the dosage of the system as needed for particular level of pain and anatomical sites of interest. It should be appreciated, however, that onset time as well as duration of analgesic effect of the transdermal composition of the present invention will vary from subject to subject as well as on the basis of the site of application, and properties of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds.

Generally, the concentration of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds can range, on a weight basis, from about 1% to about 30% of the total composition, preferably from about 3% to about 20%, and more preferably from about 5% to about 15%.

Pharmaceutically Acceptable Carriers

The transdermal compositions of the present invention also includes a pharmaceutically acceptable carrier which is capable of transdermal delivery of the amine containing compound having biphasic solubility. As used herein, the term "pharmaceutically acceptable carrier suitable for trans-

dermal delivery" includes a carrier capable of delivering the amine containing compound transdermally as defined above. Suitable carriers for transdermal delivery of pharmaceuticals are described in U.S. Pat. No. 5,446,070, the contents of which are incorporated herein by reference. Briefly, pharmaceutically acceptable carriers of the present invention include any suitable finite (i.e., solid) or non-finite (i.e., non-solid, such as liquid or semi-liquid) carrier including liquids, semi-liquids or solid carriers, such as a bioadhesive. Thus, the amine containing compounds having biphasic solubility may be admixed with a pharmaceutically acceptable carrier such as a cream, gel, emulsion, lotion, salve, paste, plaster, ointment, spray solution, or any other "non-finite" carrier known in the art of pharmaceutical delivery. For example, the base of a non-finite carrier may be lipid including phospholipids such as lecithins; fatty oils; lanolin; vasoline; paraffins; glycols; higher fatty acids; and higher alcohols.

The term "bioadhesive" as used herein includes an adhesive which attaches to a biological surface such as skin or mucosal tissue. Preferably, the bioadhesive of the present invention is self-adhesive in that it attaches to the site of interest without the need to reinforce its attachment by way of another adhesive. Suitable bioadhesive include natural or synthetic polysaccharides such as cellulose derivatives including methylcellulose, cellulose acetate, carboxymethylcellulose, hydroxyethylcellulose and the like; pectin; a mixture of sulfated sucrose and aluminum hydroxide; hydrophilic polysaccharide gums including natural plant exudates, such as karaya gum, ghatti gum, tragacanth gum, xanthan gum, jaraya gum and the like; seed gums including guar gum, locust bean gum, psillium seed gum and the like; and lecithins such as soya lecithin. In addition to the above ingredients, compositions of the present invention may also include other ingredients such as various pharmaceutically acceptable additives available to those skilled in the art. These additives include binders, stabilizers, preservatives, flavorings, fragrances, and pigments.

In another embodiment, the pharmaceutically acceptable carrier of the present invention includes van pen cream (cetyl alcohol, stearyl alcohol, steric acid, glycerol monostearate, isopropyl myristate, soya lecithin, BHT alcohol 95%, simethicone, sodium hydroxide 30% solution, polyoxyl stearate, edetate disodium 5%, purified water, urea).

Other Pharmaceutical Compounds

In another aspect, the invention features a transdermal composition suitable for transdermal delivery, which includes a therapeutically effective amount of a pharmaceutical compound (e.g., a serotonin specific reuptake inhibitor, a mood stabilizing compound, a dopamine compound, a compound suitable for treating attention deficit hyperactivity disorder, a compound suitable for treating hypertension and akathisia, an analgesic compound, or a compound used in the treatment of impotence) and a pharmaceutically acceptable carrier suitable for transdermal delivery of the pharmaceutical compound.

As used herein, the term "pharmaceutical compound" includes compounds suitable for treating a targeted condition and capable of being delivered in active form, in vivo. Examples of pharmaceuticals include drugs, enzymes, chemical compounds, combinations of chemical compounds, biological macromolecules and analogs thereof. Examples of pharmaceutical compounds are described in detail below.

In one embodiment of the invention, the pharmaceutical compound is a serotonin specific reuptake inhibitor (SSRI).

SSRIs are commonly prescribed for patients with diagnoses of mood disorders, some forms of anxiety disorder (particularly panic disorder), obsessive compulsive disorders, some forms of menopausal disorders, and eating disorders (especially bulimia nervosa). Examples of such SSRIs include sertraline (sold under the trade name Zoloft), paroxetine (sold under the trade name Paxil), fluoxetine (sold under the trade name Prozac), venlafaxine (sold under the trade name Effexor), and fluvoxamine (sold under the trade name Luvox).

In another embodiment of the invention, the pharmaceutical compound is a mood stabilizing medication, such as carbamazepine (sold under the trade name Tegretol) and valproic acid (sold under the trade name Depakote). These agents are used frequently in psychiatric practice as either augmentation medications (to render antidepressants more effective) or as anti-manic medications in the treatment of bipolar mood disorder. Mood stabilizing medications are also used in neurologic practice for the treatment of seizure disorders and for the treatment of certain pain disorders.

In yet another embodiment of the invention, the pharmaceutical compound is a compound used for treating Attention Deficit Hyperactivity Disorder (ADHD), one example of which is permoline, sold under the trade name Cylert. Permoline is a medication that is used in the treatment of Attention Deficit Hyperactivity Disorder in children and adults. It is practically insoluble in water, but soluble in ethylene glycol and lipids, making it a good candidate for transdermal administration.

In a further embodiment of the invention, the pharmaceutical compound is a dopamine compound, used for treating Parkinson's disease, examples of which are pergolide, sold under the trade name Permax and bromocriptine mesylate, sold under the trade name Parlodel.

In yet another embodiment of the invention, the pharmaceutical compound is a compound used for treating hypertension and akathisia, one example of which is propranolol, sold under the trade name Inderal.

In yet a further embodiment of the invention, the pharmaceutical compound is a compound used in the treatment of impotence such as sildenafil, sold under the tradename Viagra. It is believed that transdermal administration of sildenafil may be useful, for at least some subjects, as compared to oral administration which has been found, in at least some situations, to be associated with gastrointestinal side effects.

Methods For Preparing The Transdermal Compositions

Another embodiment of the present invention provides a method for preparing the above described transdermal compositions, by admixing a therapeutically effective amount of the amine containing compound having biphasic solubility, optimally an agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant, optimally an anti-inflammatory compound with the carrier suitable for transdermal delivery of the amine containing compound.

In one embodiment of the present invention, a transdermal composition is prepared by dispersing or dissolving crushed tablets, capsules or other preparation(s) of the amine containing compound having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds, which were intended for oral delivery, in a gel formed of soya lecithin and isopropyl palmitate or isopropyl myristate, alcohol, or ethoxy diglycol. In another embodiment of the present invention, Pluronic gel, formed of Pluronic such as Pluronic F127, potassium sorbate and water is used.

In a particular embodiment of the present invention, a transdermal composition including a combination of dox-

épin with guaifenesin is useful for treating pain. It is believed that transdermal administration of such combination can be advantageous, for at least some patients, as compared to oral administration, because higher local pharmaceutical concentrations at the site(s), e.g., of injury, can be achieved yielding an improved therapeutic response without systemic side effects such as weight gain, drowsiness, gastrointestinal upset and/or other known side effects of these pharmaceuticals.

Methods For Use

In one embodiment, the invention feature methods for treating pain in a subject in which the subject is contacted with a transdermal composition including an amine containing compound having biphasic solubility in an amount effective to treat pain in the subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound to thereby treat pain in the subject. In a preferred embodiment, the transdermal composition is applied to the skin of the subject as often as needed for the alleviation of pain. For example, the transdermal composition may be applied daily, weekly, monthly, yearly, for a length of time sufficient to alleviate pain.

Detailed examples of the preparation are provided below, along with examples of results obtained from transdermal administration to human patients. Preferably, a gel preparation is applied to the skin at the site or sites of pain. Patients can be evaluated by means of a structured evaluation form, e.g., completed at a frequency of at least one time per week. Evaluation of patients are for the present symptoms as well as any side effects from currently administered medications. This makes it possible to note changes on an ongoing basis.

Compositions of the invention can be self-administered doses in the form of a gel applied to the skin by the patient, or be implemented by providing a transdermal preparation in premeasured doses preferably in connection with an adhesive or other covering or patch so that the dosage may be administered e.g., by placing the adhesive patch on the skin of the patient. Although some embodiments of the invention have been described in connection with positioning the pharmaceutical gel on the arm of a patient, other positioning on the skin of a patient can also be used. Because, depending on the formulation, speed or duration of transdermal delivery may vary as function of skin location, in one embodiment the location of the skin to which the pharmaceutical is applied is selected so as to relatively increase or decrease the delay, speed, duration, or rate of delivery of the pharmaceutical, either with respect to a particular tissue or systemically.

For example, when a rapid rise in blood serum levels is desired, a placement which enhances delivery rate, such as behind the ear, can be used. When it is desired to enhance dose or delivery rate locally, the transdermal formulation may be positioned adjacent the desired treatment area. Membranes or matrices, such as a polymer matrix, may be used to limit or control delivery rates. In addition to transdermal gel or patch delivery, delivery of the transdermal or aerosol formulation can be achieved, e.g. by administration as nose drops, eardrops, eyedrops and/or suppositories.

In one embodiment, medications dispensed in transdermal gel form will be dispensed in unit doses, such as blister packs. The gel will be extruded from the blister pack, and rubbed on the administration site. The dosage will be adjusted by varying the number of unit dose applied. This will ensure accurate dosimetry and will avoid contamination of the gel.

Methods For Selecting A Compound Suitable For Treating Pain

In a further aspect, the invention features a method for selecting a compound suitable for treating pain in a subject. The method includes transdermally administering an amine containing compound having biphasic solubility to a subject; and determining whether pain is treated in the subject to thereby select a compound suitable for treating pain in a subject. In a preferred embodiment, the method can further include modeling the compound using a computer equipped with a three-dimensional chemical structure modeling program (e.g., Molecules-3D Professional Edition, version 2.60, copyright 1991-1998, Molecular Arts Corp., © 1994-1998 WCB/McGraw Hill); and determining whether the three-dimensional chemical structure of the compound possesses sufficient characteristics to be useful as a sodium or a calcium channel blocker, thereby selecting a compound suitable for treating pain in a subject.

The effectiveness of the amine containing compound having biphasic solubility to treat pain can be tested in vitro or in vivo. An animal model for pain, e.g., such as the one described in Kral M. G. et al. (1999) Pain 81(1-2): 15-24 can, for example, be used for testing such compounds.

Preferred Transdermal Compositions

In certain preferred embodiments, the transdermal compositions of the present invention include lamotrigine and doxepin; topiramate and chlorzoxazone; topiramate and guaifenesin; topiramate and doxepin; topiramate and naproxen; doxepin and chlorzoxazone; lamotrigine and guaifenesin; lamotrigine, doxepin, and guaifenesin; or lamotrigine, doxepin, and chlorzoxazone.

This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application, as well as the Figures are incorporated herein by reference.

EXAMPLES

Example 1

One hundred grams of lecithin soya (granular) and 0.66 grams sorbic acid (NF-FCC powder) were dispersed in 100 grams (117 milliliters (mL)) of isopropyl palmitate NF and allowed to stand overnight. Approximately 220 milliliters of lecithin-isopropyl palmitate in a form of a liquid of a syrup consistency was formed.

Example 2

One hundred grams of lecithin soya (granular) and 0.66 grams sorbic acid (NF-FCC powder) is dispersed in 100 grams (117 milliliters) of isopropyl myristate NF and allowed to stand overnight. Approximately 220 milliliters of lecithin-isopropyl myristate in a form of a liquid of a syrup consistency was formed.

Example 3

A beaker was prepared by measuring to a volume of 100 milliliters. It was considered important to measure the volume accurately rather than using beaker markings. An amount of Pluronic F127 NF (20 grams for a 20 percent gel, 30 grams for a 30 percent gel, 40 grams for a 40 percent gel) was mixed with 0.3 grams potassium sorbate NF. Refrigerated purified water was added in an amount sufficient to bring the volume to 100 milliliters. When all of the granules had been wet the gel was refrigerated. Solution took place upon cooling, taking 12 to 24 hours. The resulting 100

milliliters of Pluronic gel was kept refrigerated, since the gel will solidify at room temperature.

Example 4

Nine grams of carbamazepine in tablet form was ground in mortar and pestle. 4.3 milliliters of ethoxy diglycol was added and mixed to form a creamy paste. 13.2 milliliters of soya lecithin was added and mixed until smooth. The resulting 24 cc of solution was put into a 60 cc syringe. About 36 cc Pluronic F127 gel 20 percent (made according to Example 3) was placed in another syringe. The material was mixed well between syringes to yield 60 cc of carbamazepine organogel having a strength of 150 milligrams (mg) per milliliter. In some cases, the mixture was run through an ointment mill to reduce particle size.

Example 5

Sixty 100 milligram tablets of bupropion were ground and strained to form a fine powder. The bupropion powder was dissolved in 30 cc purified water, placed in a filter and washed with 10 to 20 cc purified water. The filtrate was used to make a 20 percent Pluronic gel using the procedures from Example 3, substituting filtrate for an equivalent volume of water, and stored in a refrigerator. Thirteen milliliters of soya lecithin was mixed with one-half the bupropion Pluronic gel and mixed between syringes to form a first batch. Thirteen milliliters of soya lecithin was mixed with the second half of the bupropion Pluronic gel and mixed between syringes to form a second batch. To each batch was added sufficient Pluronic gel F127 (made according to example 3) to yield a total of two 60 cc batches of bupropion HCl organogel having a strength of 15 milligrams per milliliter.

Example 6

600 milligrams of fluoxetine HCl (in the form of thirty 20 milligram capsules) was placed in a beaker and dissolved in approximately 18 cc of 95 percent ethyl alcohol. The solution was filtered through a filter funnel using fine filter paper. The residue was washed with 95 percent alcohol. The filtrate was heated, maintaining a temperature less than 85° C., to evaporate the alcohol to concentrate to 1 to 2 milliliters. 600 milligrams of isopropyl palmitate was combined with 600 milligrams of soya lecithin (granular), set aside and allowed to liquefy. Upon liquefaction, a thick syrupy consistency was obtained. 1.2 grams of the mixture was drawn into a 10 milliliter syringe and the alcoholic solution of fluoxetine HCl was drawn into another syringe. The two syringes were attached together with a Luer-Luer adapter and the gel was thoroughly mixed. All of the organogel was then transferred into one syringe and the empty syringe was disconnected. Sufficient quantity of 20 percent Pluronic F127 gel (formed as described in Example 3) was drawn into the empty syringe to make a total of 6 milliliters when added to the volume in the other syringe. A Luer-Luer adapter was attached and the contents of the two syringes was remixed until a smooth creamy mixture was obtained. All the mixture was transferred into one syringe, the empty syringe was removed and the Luer-Luer adapter was removed.

A Luer-oral adapter was attached to the mixture and transferred to six 1 milliliter oral syringes, was filled with 1 milliliter of the gel. In this way, each syringe contained five 20 milligram doses, or ten 10 milligram doses to yield a total of 60 doses of fluoxetine in lecithin organogel having a strength of 10 milligrams per 0.1 milliliters.

Example 7

Twelve 250 milligram tablets of nefazadone were crushed in a mortar and pestle and put through a strainer. 4.8

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milliliters of ethoxy diglycol (8 percent) was added and mixed. In cases in which all particles were not dissolved, 2 milliliters of Pluronic were added and mixed. 13.6 milliliters of soya lecithin were added and mixed. The resulting mixture was put into syringes with a Luer adapter and mixed well. Sufficient Pluronic F127 gel, prepared according to Example 3, was added to achieve a volume of 60 cc and mixed well to yield 60 cc of nefazadone organogel having a strength of 50 milligrams per milliliter.

Example 8

Thirty 40 milligram tablets of paroxetine were crushed and run through a strainer, discarding green coating material. 4.8 milliliters of ethoxy diglycol was added to the powder and mixed in a mortar and pestle. Forty milliliters of Pluronic F127 gel 20 percent, formed according to Example 3, was added in graduated amounts to the powder and mixed until smooth using a spatula. 13.2 milliliters of soya lecithin was added and mixed well and the resulting material placed into syringes and sufficient quantity of Pluronic gel was added to bring the volume to 60 milliliters. In those such cases where particle size of the resulting material was too large, the cream was run through an ointment mill to yield 60 milliliters of paroxetine organogel having a strength of 20 milligrams per milliliter.

Example 9

Thirty 100 milligram tablets of sertraline were crushed into a fine powder and strained, discarding the yellow coating. Sufficient amount of Pluronic F127 gel 20 percent (formed according to Example 3) was added to achieve a volume of 38 milliliters and mixed well in a mortar and pestle until a smooth cream was achieved. This material was placed into syringes and mixed between the syringes to obtain a compact cream. 13.2 milliliters of soya lecithin was added and mixed well between the syringes using about 20 pumps. Sufficient quantity of Pluronic F127 gel 20 percent was added to yield 60 milliliters of sertraline gel having a strength of 15 milligrams per milliliter.

Example 10

Venlafaxine hydrochloride has a solubility in water of 572 mg/mL (adjusted to ionic strength of 0.2 M with sodium chloride). Forty-five 100 milligram tablets of venlafaxine were crushed and put through a strainer. The powder was dissolved in 15 cc purified water, the solution placed into a filter and washed with 10 cc purified water. The filtrate was used to make a 20 percent Pluronic gel using the procedures of Example 3 (substituting the filtrate for an equivalent amount of water) and placed into a refrigerator overnight. 13.2 milliliters of soya lecithin were drawn into a syringe with a Luer loc. The venlafaxine Pluronic gel was drawn into another syringe coupled to the first syringe and mixed well. Sufficient Pluronic F127 gel was added to achieve a volume of 60 cc with a strength of 75 mg. per cc.

Example 11

15 grams of sodium valproate (Depakote) was ground in mortar and pestle. 4 mL of ethoxy diglycol was added and mixed well to form a creamy paste. 19.8 mL of soya lecithin was added and mixed until smooth. The resulting 24 cc of solution was put into 2 syringes with a Luer Loc and mixed well. The mixture was divided so that half is in each syringe. Using another 60 cc syringe, Pluronic 30% gel was added to each to bring each syringe to a volume of 45 mL.

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Example 12

Paroxetine hydrochloride has a solubility in water of 5.4 mg/mL. Paroxetine (Paxil) gel was prepared, according to the procedures of example 8. A dosage of 40 mg per day was self-administered by a 59 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 210 days, blood was drawn and blood serum level of Paxil was determined to be 0 nanograms (ng) per mL, while typical reference levels are 49 ± 26 ng/mL, indicating possible poor absorption or lab error. Clinical evaluation of the patient over a 210 day period of such transdermal administration indicated benefit to patient without GI side effects similar to that noted with oral preparation.

Example 13

Sertraline hydrochloride is slightly soluble in water and isopropyl alcohol and sparingly soluble in ethanol. Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 100 mg per day was self-administered by a 54 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 19 days, blood was drawn and blood serum level of Zoloft was determined to be 5 ng/mL, while typical reference levels are 30–200 mg/mL indicating possible limited absorption or lab error.

Example 14

Fluoxetine hydrochloride has a solubility in water of 14 mg/mL. Fluoxetine (Prozac) gel was prepared, according to the procedures of example 6. A dosage of 20 mg per day was self-administered by a 54 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7 days, blood was drawn and blood serum level of fluoxetine was determined to be 45 ng/mL, while the plasma level of the primary active metabolite norfluoxetine was also 45 ng/mL. There was evidence of patient benefit from the clinical evaluation.

Example 15

Carbamazepine is practically insoluble in water and soluble in alcohol and in acetone. Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 400 mg per day was self-administered by a 55 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 120 days, blood was drawn and blood serum level of Tegretol was determined to be 4.6 micrograms (μ g) per mL, while typical therapeutic levels are 4–10 μ g/mL indicating good absorption. There were no GI side effects and the patient demonstrated clinical improvement.

Example 16

Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 200 mg per day was self-administered by a 53 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 60 days, blood was drawn and blood serum level of Tegretol was determined to be 10.8 μ g/mL, while typical therapeutic levels are 4–10 μ g/mL indicating excellent absorption. There were no GI side effects and the patient demonstrated clinical improvement.

Example 17

Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 50 mg per day was

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self-administered by a 53 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 63 days, blood was drawn and blood serum level of Zoloft was determined to be 23 ng/mL, while typical reference levels are 30–200 mg/mL. The patient demonstrated a good clinical response without GI side effects.

Example 18

Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 200 mg per day was self-administered by a 47 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 91 days, blood was drawn and blood serum level of Tegretol was determined to be less than 0.5 μ g/mL, while typical therapeutic levels are 4–10 μ g/mL, indicating poor absorption, lab error, or patient non-compliance.

Example 19

Bupropion is highly soluble in water. Bupropion (Wellbutrin) gel was prepared, according to the procedures of example 5. A dosage of 100 mg per day was self-administered by a 47 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 44 days, blood was drawn and blood serum level of Wellbutrin was determined to be less than 0.5 ng/mL, while typical therapeutic levels are 10–30 indicating poor absorption, lab error, or patient non-compliance.

Example 20

Fluoxetine gel was prepared, according to the procedures of example 6. Typically, a total daily adult dosage of fluoxetine as applied to the skin according to the present invention is between about 20 mg and 200 mg, more preferably between about 120 mg and about 200 mg. Dosages for non-adults and/or non-human mammals may need to be adjusted, e.g. proportionally to body weight. A dosage of 20–60 mg per day was self-administered by 5 patients, including that of example 13 and also including a 44 year old male patient, a 53 year old female patient, a 47 year old male patient and a 36 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 30–180 day period of such transdermal administration indicated a clinical response ranging from complete remission of symptoms to moderate improvement.

Example 21

Fluoxetine gel was prepared, according to the procedures of example 6. A dosage of 80–160 mg per day was self-administered by a 50 year old female by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7 days at the 80 mg dosage level blood was drawn and the blood serum of fluoxetine was determined to be 34 ng/mL fluoxetine and 25 ng/mL norfluoxetine, while typical reference levels are 50–480 ng/mL, indicating good absorption. There was evidence of patient benefit from the clinical evaluation. The dosage was then increased to 160 mg per day and administered by the same method. After 7 days at the 160 mg dosage level blood was drawn and the blood serum level of fluoxetine was determined to be 90 ng/mL fluoxetine and 25 ng/mL norfluoxetine, indicating good absorption. There was evidence of increased patient

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benefit at this higher dosage level which correlated positively with the higher plasma level. The patient has been receiving the medication continuously for a period of 5 months.

Example 22

Fluoxetine gel was prepared, according to the procedures of example 6. A dosage of 80–160 mg/day was self-administered by a 38 year old female by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7 days at the 80 mg dosage level, blood was drawn and the blood serum level of fluoxetine was determined to be 25 ng/mL of fluoxetine and 25 ng/mL norfluoxetine. There was evidence of patient benefit from the clinical evaluation. The dosage was then increased to 160 mg per day and administered by the same method.

Example 23

Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 50–200 mg per day was self-administered by 6 patients, including those of examples 12 and 16 and also including a 60 year old male patient, a 53 year old male patient, a 48 year old male patient, a 38 year old male patient and a 47 year old male patient, by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 7–90 day period of such transdermal administration indicated responses ranging from complete resolution of depression to no noticeable response.

Example 24

Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 200–400 mg per day was self-administered by 6 patients, including those of examples 14, 15 and 17, and also including a 48 year old female patient, a 48 year old male patient and a 54 year old female patient, by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. The clinical evaluation of the patients over a 30–300 day period of such transdermal administration indicated responses ranging from moderate improvement to no positive clinical response.

Example 25

Paroxetine (Paxil) gel was prepared, according to the procedures of example 8. A dosage of 20 mg per day was self-administered by the patient of example 12 as well as by a 15 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. Clinical evaluation of the patients over a 30–210 day period of such transdermal administration indicated equivocal clinical improvement of the depression which may (or may not) have been related to the transdermally administered Paxil.

Example 26

Five 150 mg tablets of amitriptyline were crushed and run through a strainer. The powder was put into syringes with a Luer Loc and mixed well with 2 mL ethoxy diglycol. About 6 mL Pluronic Gel 20% was added and mixed well. 6.6 mL Soya Lecithin was added and mixed well. This mixture was thinned to 30-mL total volume with Pluronic Gel 20% and mixed well. The resulting mixture having a strength of 25 mg/mL was placed in appropriate dispensing device.

Example 27

Amitriptyline (Elavil) gel was prepared, according to the procedure of example 26. A dosage of 25 mg per day was self-administered by a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 100 day period of such transdermal administration indicated an apparently good clinical response, comparable to that achieved with oral medication.

Example 28

Trazodone (Desyrel) gel was prepared, according to a procedure similar to that of example 7. A dosage of 50–150 mg per day was self-administered by 2 patients, including a 36 year old female patient and a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 42–90 day period of such transdermal administration indicated a good to excellent clinical response.

Example 29

Venlafaxine (Effexor) gel was prepared, according to a procedure similar to that of example 9. A dosage of 150–225 mg per day was self-administered by 2 patients, including a 54 year old female patient and a 55 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 15–165 day period of such transdermal administration indicated a response ranging from no clinical improvement to mild clinical improvement.

Example 30

Propranolol (Inderal) gel was prepared, according to a procedure similar to that of example 8 to produce a gel having a strength of 40 mg of propranolol per mL of gel. A dosage of 80 mg per day was self-administered by 2 patients, including a 36 year old female patient and a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 100 day period of such transdermal administration indicated results comparable to those achieved with oral medication.

Example 31

Bupropion (Wellbutrin) gel was prepared, according to a procedure described in example 5. A dosage of 150–200 mg per day was self-administered by 3 patients, including that of example 18, and also including a 38 year old male patient and a 53 year old female patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 5–45 day period of such transdermal administration indicated equivocal results.

Example 32

Valproic acid (Depakote) gel was prepared, according to a procedure similar to that of example 4. A dosage of 1000 mg per day was self-administered by a 38 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal

side effects were reported. Clinical evaluation of the patients over a 30 day period of such transdermal administration indicated results comparable to those achieved with oral medication.

Example 33

Valproic acid (Depakote) gel was prepared according to the procedure of example 11. A dosage of 500–1000 mg was self administered by two male patients, ages 41 and 49. Administration was by application to the skin, for a period of at least one hour. Significant skin irritation occurred with one patient, but no gastrointestinal side effects were reported. Clinical evaluation of the patients over a period of two months revealed improvement, but upon longer term follow-up it appeared that other factors may have been responsible. After 28 days, blood was drawn and a serum valproic acid level of 26 $\mu\text{g/mL}$ was obtained for the 49 year old patient (while taking 250 mg twice daily), with a therapeutic reference range of 50–150 $\mu\text{g/mL}$. This indicated poor to fair absorption, and the dosage was raised to 500 mg twice daily, with a further improvement in clinical response. The 41 year old patient reported a good clinical response to an initial dosage of 250 mg administered twice daily, but a serum valproic acid level of only 1 $\mu\text{g/mL}$ was obtained. The dosage was increased to 500 mg twice daily, and a similar serum valproic acid level was obtained. The disparity between the clinical response and the plasma level might be explained either by laboratory error or placebo effect.

Example 34

A gel containing reboxetine (sold under the trade name Edronax) is prepared according to a procedure similar to that described in example 5 but using reboxetine in place of bopropion. The resulting mixture will be self administered by patients by application to the skin for a period of at least 1 hour. No skin irritation or gastrointestinal side effects are expected. Clinical evaluation of patients over a 5–45 day period of such transdermal administration is expected to indicate a good response to treatment.

Example 35

Nefazodone (Serzone) gel was prepared, according to a procedure described in example 7. A dosage of 100 mg per day was self-administered by a 61 year old (male, female) patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 21 day period of such transdermal administration indicated a good response to treatment.

Example 36

1 gram of permoline tablets are crushed in a mortar and then dissolved in propylene glycol, just sufficient to effect dissolution. 3 mL of propylene glycol or 95% ethyl alcohol is added to form a paste. 6.6 mL soya lecithin is added to the mixture in the mortar. The mixture is placed in two syringes with a Luer Loc and mixed thoroughly. Each syringe is filled to 30 mL Pluronic F127 20% gel and mixed between syringes to produce a mixture having a strength of 33 mg/mL. The mixture is put in an appropriate dispensing device.

Example 37

A 16-year-old female with an established diagnosis of Attention Deficit Disorder had been treated successfully

with oral pemoline (Cylert) for about 6 months. To potentially decrease the risk of liver damage associated with long-term use, pemoline prepared according to the procedure of example 36 will be administered transdermally, by application to the skin in the post auricular region for a period of at least one hour, at two sites, twice daily. No skin irritation is expected. The clinical results are expected to be comparable to those obtained with the oral medication, although the dosage may have to be adjusted upwards to achieve adequate plasma levels, and more time may be required to achieve satisfactory plasma levels.

For psychiatric patients, some have received two or more psychopharmaceuticals, and in some cases, two or more of the above examples describe different evaluations for the same period of administration of a psychopharmaceutical agent.

Of the patients who have received prescriptions for one or more of the medications as described in the examples above, each had previously demonstrated a significant intolerance to oral administration of one or more medications, prior to instituting transdermal administration. The laboratory measures of plasma blood levels described above for transdermally administered fluoxetine and carbamazepine are believed to demonstrate good absorption transdermally using lecithin organogel matrix as the vehicle. Valproic acid and sertraline do not appear to be absorbed well or reliably. Valproic acid appears to cause skin irritation in some patients necessitating discontinuation. Both the laboratory measure of Bupropion and the patient clinical responses indicated poor or equivocal absorptions and results. Patient tolerance of transdermal administration has been good to excellent. Patients in the example above who suffered very severe GI side effects using oral preparations were more tolerant of the inconvenience of rubbing on the gel than were patients who had experienced only mild to moderate side effects. In general, more highly motivated and treatment-compliant patients also had a higher rate of sustained compliance.

Patients in the examples above were evaluated by means of a structured evaluation form depicted in FIG. 1, which was completed at a frequency of at least one time per week for each patient receiving transdermal medication according to the present invention. The patients were evaluated both for all present psychiatric symptoms as well as any side effects from currently-administered medications. In general, it is believed that patients with the most clear cut and uncomplicated diagnosis of major depression experienced the best results. In general, patients with severe personality disorders or with concealed substance abuse disorders did less well.

Example 38

1800 mg of gabapentin in powder form is dissolved with 1 mL propylene glycol in syringes with a Luer Loc. 6.6 mL of Soya lecithin is added and mixed thoroughly between syringes. The resulting material is placed in a device for dispensing measured amounts.

Example 39

Gabapentin mixtures of 2% and 4% will be prepared by substituting 1200 mg gabapentin or 600 mg gabapentin in place of 1800 mg gabapentin, in example 38.

Example 40

Gabapentin, prepared according to Example 38 or 39, will be combined with either 3% or 5% Lidocaine in varying ratios.

Example 41

4% gabapentin, prepared according to Example 38 or 39, will be combined with 7% carbamazepine and 7% amitriptyline.

Example 42

2% gabapentin, prepared according to Example 38 or 39, will be combined with 2% carbamazepine and 1% Piroxicam, which is expected to yield better penetration into muscle tissue.

Example 43

Gabapentin, prepared according to Example 38 or 39, in concentrations ranging from 2%–6% will be combined with clonidine in concentrations between 0.2% and 0.3%.

Example 44

A 56-year-old woman had painful upper and lower extremity spasms as a result of spastic quadriparesis resulting from an injury. Oral gabapentin, an anticonvulsant, had been administered previously, but had caused a "drugged" feeling, one of the commonly reported side effects with this agent. It was believed that use of transdermal gabapentin might provide local relief by achieving high local tissue concentrations near the site of administration without correspondingly elevated blood plasma levels. It is known that other anticonvulsants, such as carbamazepine, are useful in reducing neurogenic pain. Gabapentin's solubility in water exceeds 10%, making systemic absorption less likely. Gabapentin prepared according to the procedure of example 38 was self-administered by application to the skin in the area of pain. The patient reported moderate relief of spasms over a period of one week, with no systemic side effects and no report of skin irritation.

Example 45

Six grams of amitriptyline powder was placed in 40 milliliters of Pluronic F127 33% gel and placed under refrigeration to dissolve. Two milliliters of ethoxy diglycol was added to 4.8 grams of carbamazepine and mixed to form a smooth paste. 16.4 grams of soya lecithin was added to the resulting paste and mixed well. The dissolved amitriptyline composition was added to the carbamazepine composition and sufficient Pluronic F127 20% was added to make 120 milliliters and the resulting composition was mixed well to yield a composition having 5% amitriptyline and 4% carbamazepine.

Example 46

6 grams of doxepin was added to 20 milliliters Pluronic 33% F127 and put into a refrigerator to dissolve. 24 grams of ketoprofen and 12 grams of guaifenesin was added to 10 milliliters of 95% alcohol and mixed well. 26.4 milliliters of soya lecithin was added and mixed well and the doxepin composition was mixed with the ketoprofen/guaifenesin composition. The resulting mixture was added to sufficient Pluronic 33% to yield 120 milliliters. The resulting composition was mixed well to yield a composition having about 20% ketoprofen, 5% doxepin and 10% guaifenesin.

Example 47

6 grams of doxepin was added to 26 milliliters Pluronic 33% and refrigerated to dissolve. 2 milliliters ethoxy diglycol was added 4.8 grams carbamazepine and mixed. The

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resultant mixture was added to 24 grams ketoprofen and six milliliters alcohol and the result was mixed well. 26.4 milliliters soya lecithin was added to the ketoprofen composition and mixed well. The doxepin composition was mixed with the carbamazepine/ketoprofen composition and sufficient Pluronic 33% was added to yield 120 milliliters. The resultant composition was mixed well to yield a composition having about 20% ketoprofen, 4% carbamazepine and 5% doxepin.

Example 48

0.15 grams sildenafil was crushed and strained and dissolved in 5 milliliters Pluronic 20% F127 and mixed between syringes. 2.2 milliliters of soya lecithin was added and mixed. Sufficient Pluronic 20% was added to yield 10 milliliters and the resultant composition was mixed well to yield a composition having the strength of about 15 milligrams per milliliter.

Example 49

A mixture of Sildenafil 15 mg/ml was applied to the penis and scrotum of a 51 year old male. An immediate and strong

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erection resulted with sexual stimulation, without any irritation or burning. It is believed the composition will possess the therapeutic results claimed for orally administered Sildenafil, without any time delay, without any systemic GI side effects, and possibly without the degree of drug interaction with nitrates used in cardiac disease. It is believed that this will contribute both to the convenience of use of the pharmaceutical and to its safety.

Example 50

Compositions according the examples 45 through 47, 53, 55 were transdermally applied to numerous patients, for the purpose of treating pain including as described in other examples herein, with the results summarized in Table I below. The meaning of certain entries in Table I is indicated in Table II below. Blank results indicate no treatment at the pertinent site for this patient. Where a given line of Table I shows more than one site, one "best" (greatest pain relief) result if shown in bold.

TABLE I

Patient	Age	Gender	Surgery	Pain	Medication Wt % in lecithin organogel						
					Ketoprofen	Gabapentinm	Piroxicam	doxepin	carbamazepine	amitriptyline	guifenesin
A	50	2	2	3	10	3	4				
B	61	1	1	3				5			
B	61	1	1	3					4		
B	61	1	1	3	10	4	3				
C	41	2	1	2					4	5	
D	53	1	2	1	10	4	1				
E	57	2	2	3	10	4		5			1
E	57	2	2	3	10	4	3				
F	38	2	2	3				10	5		5
F	38	2	2	3		4			4		
F	38	2	2	3	10	4	1		4		
G	39	1	1	2	20	4		5	4		
H	61	1	1	3	10	4	3				
I	49	1	1	3	10	4	3				
I	49	1	1	3				5	5		10
I	49	1	1	3			4		4		
J	54	1	1	3					5	5	
K	40	1	2	3				5			
K	40	1	2	3	10		3	6			
L	55	2	2	2	10	4	3				
L	55	2	2	2				5			
M	38	1	2	1				4	5		
N	47	2	1	2	20	2				5	
N	47	2	1	2	10	4	1				
O	57	2	1	2	20	4		5			
O	57	2	2	2	10	4	3				
P	51	2	2	2	15	5		5			
Q	51	2	1	2	20			5			10
R	35	1	1	2					4	5	
R	35	1	1	2	10	4	1				
S	55	1	1	2	10	4	1				
T	50	2	2	1	10	4	1				
U	45	1	2	2	10	4	3				
V	57	2	1	3					6		
V	57	2	1	3	10	4	1				
W	35	1	2	1	10	4	1				
X	46	1	1	3	10			5	4		
Y	48	1	1	3				5			
Y	48	2	1	3	10	4	1				
AA	53	2	2	1	10	4	1				
BB	58	2	1	3	20	4			4	Hand	1
CC	59	1	1	2				5			
CC	59	1	1	2	10	4	1				
CC	59	1	1	2	10	4	5				

TABLE I-continued

Patient	Duration	Result (Best result in Bold)									
		shoulder	back	neck	elbow	Knee	Wrist	Arm	Ankle	Hip	Leg
DD	58	1	1	2	10	4	3				
EE	45	2	2	2	10	4	3				
FF	44	2	1	3	10	4	3				
GG	35	1	1	3	20	4					
A	2		0								
B	4				2.0						
B	12	2.0	2.0	2.0	2.0						
B	6							3.0			
C	2		1.0								
D	1			.0							
E	1		2.0			1.5					1.0
E	2	10	2.0				1.0				
F	2	2.0			3.0						
F	8	2.0						1.5			
F	4	2.0						1.0			
G	6					3.0					
H	4		2.0								
I	12						2.0				
I	1						1.0				
I	2						3.0				
J	2		1.5								
K	6	4.0									
K	4	1.0									
L	8	1.0							0		
L	6		3.0					.0		15	2.0
M	2	1.5					.0				
N	3	30	3.0	4.0		1.0					
N	2.0	.0		2.0			2.0				
O	24	2.0		3.0							
O	24	1.0	.0								
P	2		4.0								
Q	1		2.0								
R	0					1.5					
R	1					.0					
S	16		1.0								
T	16					2.0	1.0		2.0		
U	2		.0								
V	8					3.0					
V	3					1.0					
W	8		1.0								
X	8		2.0	2.0	20						
Y	4	2.0	2.0								
Y	4				1.5		1.5			.0	
AA	4		1.0								
BB	8		2.0							2.0	
CC	2			2.0		2.0			2.0		
CC	20		1.0	2.0		3.0	2.0				
CC	1					3.0			3.0		
DD	12			1.0			2.0				
EE	24	1.5		1.0							
FF	20	2.0									
GG	4				1.0		1.0				

Medication
Wt % in lecithin organogel

Patient	Age	Gender	Surgery	Pain	Ketoprofen	Gabapentinm	Piroxicam	doxepin	carbamazepine	amitriptyline	guifenesin
GG	35	1	1	3				5			
GG	35	1	1	3	20				5	5	
GG	35	1	1	3	20			5	5		
GG	35	1	1	3		5		5			10
HH	40	1	2	2	10	4	3				
II	40	1	2	3				5			
II	40	1	1	3	10	4	3	5			
JJ	45	1	2	2	10	4	3				
KK	37	2	2	2	10	4	1				
LL	54	1	1	3	10	4	3				

-continued

LL	S4	1	1	3				4	5		
Result (Best result in Bold)											
Patient	Duration	shoulder	back	neck	elbow	Knee	Wrist	Arm	Ankle	Hip	Leg
GG	8				1.0		1.0				
GG	2						.0				
GG	2						2.0				
GG	2				1.0		2.5				
HH	4		1.0			1.0					
II	8		1.5								1.5
II	8		2.0								
JJ	2		1.0								
KK	8		1.0								
LL	6					1.0					
LL	2					.0					

Medication Wt % in lecithin organogel											
Patient	Age	Gender	Surgery	Pain	Ketoprofen	Gabapentinm	Piroxicam	doxepin	carbamazepine	amitriptyline	guifenesin
MM	42	2	1	3					4		
MM	42	2	1	3	10		3		4		
MM	42	2	1	3				5			
NN	41	1	2	2	10	4	3				

Result (Best result in Bold)											
Patient	Duration	shoulder	back	neck	elbow	Knee	Wrist	Arm	Ankle	Hip	Leg
MM	8		.0	4.0				2.0			1.0
MM	12		.0								
MM	4							2.0			1.0
NN	2		.0								

TABLE II

Gender:	1 = male	2 = female	
Surgery:	1 = one or more surgeries	2 = no surgeries	
Pain:	1 = mild	2 = moderate	3 = severe-sufficient to produce observed tears
Duration:	length of treatment trial in weeks		
Result:	0 = no benefit		
	1 = mild benefit		
	2 = moderate benefit (greater than 25% pain reduction)		
	3 = major benefit (greater than 40-45% pain reduction)		
	4 = almost complete relief (greater than 80% pain reduction)		

TABLE III

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Percent reported pain relief

Site	N (Number of data points)	Mild-moderate					Major	Total
		None	Mild	moderate	moderate	Major		
Wrist	13	16.7	33.3	8.3	41.7			
Shoulder	14	7.1	21.4	14.3	42.9	7.1	7.1	
Elbow	5		40	20	20	20		
Back	25	24	32	8	28	8		
Arm	7	28.6	14.3	14.3	28.6	14.3		
Neck	11	9.1	18.2		45.5	9.1	18.2	
Knee	13	15.4	46.2	15.4	7.7	15.4		

Certain results drawn from the information of Table I are summarized in Table III and IV.

TABLE IV

(percent reported pain relief)

	N	Mild-moderate				Major	Total
		None	Mild	moderate	moderate		
Best result without tricyclic	36	16.7	36.1	8.3	27.8	8.3	2.8
Best result with any tricyclic	20	10	10	20	35	15	10

TABLE IV-continued

(percent reported pain relief)							
	N	None	Mild	Mild- moderate	moderate	Major	Total
Either tricyclic -sole agent	7		14.3	14.3	42.9	14.3	14.3
Best result with ketoprofen	25	16	44	4	28	8	
gabapentin piroxicam							
Best result without doxepin	43	18.6	32.6	14	23.3	7	4.7
Best result with doxepin	13		7.7	7.7	53.8	23.1	7.7

Example 51

A 51 year old female administered a composition prepared according to example 46, containing 20% ketoprofen, 5% doxepin, and 10% guaifenesin to her back for a period of 2 weeks. She reported moderate pain relief, lasting several hours, after each application. She reported no skin irritation nor any other side effects. Oral medications had produced no relief, and had caused significant GI side effects.

Example 52

A 34 year old man administered a composition containing 20% ketoprofen, 4% carbamazepine, and 5% doxepin to a very severely scarred wrist that had undergone 4 surgeries for carpal tunnel syndrome. He reported moderate pain relief, lasting for several hours after each application. No other treatment, including opiate oral pain medication, had been effective in providing even minor pain relief.

Example 53

24 grams ketoprofen and sufficient guaifenesin to result in a 10% final guaifenesin concentration, was mixed well with 10 milliliters 95% alcohol. 1200 mg gabapentin was dissolved in one ml propylene glycol in a syringe with a luer loc. 26.4 ml of soya lecithin was added to the ketoprofen-guaifenesin-alcohol mixture and mixed well. The resulting mixture was added to the gabapentin-propylene glycol mixture and mixed well. 4.8 gm of carbamazepine was combined with the resultant combination and mixed well to form a smooth paste. The resulting paste was combined with the ketoprofen-guaifenesin-alcoholgabapentin mixture and mixed well with sufficient pluronic to yield 120 ml of a composition containing ketoprofen 20%, carbamazepine 4%, gabapentin 4%, guaifenesin 10%.

Example 54

A 58 year old female with damage to her cervical spinal cord with a resultant spastic quadraparesis reported moderate relief of both pain and muscle spasms when she applied a mixture prepared generally according to example 53, containing ketoprofen 20%, carbamazepine 4%, gabapentin 4%, guaifenesin 10% for a period of 8 weeks to her back and hip. She had been unable to tolerate both oral carbamazepine and oral gabapentin because of systemic side effects, including skin rash with the carbamazepine and dizziness and sedation with the gabapentin. She experienced no skin irritation nor other side effects with the transdermal formulation.

Example 55

Six grams of doxepin powder combined with 26 milliliters pluronic and placed in the refrigerator until dissolved.

1200 mg gabapentin was mixed with 1 ml propylene glycol and placed in a syringe with luer lock. 6.6 ml of soya lecithin was added and mixed well between syringes. 24 gm of ketoprofen and 8 milliliters alcohol was mixed well between two syringes with luer loc. The doxepin mixture was mixed well with the gabapentin mixture and subsequently the ketoprofen mixture was added and mixed well. Sufficient pluronic 20% (about 54 ml) was added to yield 60 ml of a composition having about 20% ketoprofen, 4% weight percent gabapentin and 5% weight percent doxepin.

Example 56

A 57 year old female applied a mixture, prepared generally according to example 55, containing ketoprofen 20%, gabapentin 4%, and doxepin 5% for a period of 8 weeks to her neck and reported major relief. She applied the same mixture to her shoulder and reported moderate relief. A mixture that substituted piroxicam for the doxepin produced only mild shoulder relief.

Example 57

A 35 year old man with a history of knee injury with vascular compromise and 3 surgeries applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% amitriptyline to his knee, and reported mild to moderate pain relief, without skin irritation nor other side effects.

Example 57A

A 41 year old woman with history of back surgery applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% gabapentin to her back for a period of 2 weeks. She reported mild pain relief.

Example 58

A 53 year old man with a history of two total bilateral knee replacements applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% amitriptyline to both knees for a period of 4 weeks. He reported no pain relief.

Example 58A

A 54 year old man with a history of 7 back surgeries applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% amitriptyline to his back for a period of 2 weeks. He reported mild to moderate pain relief, over and above that he was receiving from a transdermal opiate medication (Duragesic). He reported no side effects, and specifically no skin irritation.

Example 59

A 38 year old man with a history of shoulder strain applied a mixture, prepared generally according to example

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45, containing 4% carbamazepine and 5% amitriptyline to his shoulder for a period of 2 weeks. He reported mild to moderate pain relief, and reported no skin irritation nor other side effects.

Example 61

Sufficient carbamazepine and gabapentin was added to a combination of soya lecithin and pluronic to yield a lecithin organogel having about 4% carbamazepine and 5% gabapentin.

Example 62

A 42 year old woman with a history of 3 back surgeries and cervical degenerative disc disease applied a mixture, prepared according to example 61, containing 4% carbamazepine and 5% gabapentin to her neck and reported total relief of pain. She reported no side effects, and no skin irritation. She noted the complete and rapid resolution of a migraine like headache at the same time. Administration of the same mixture to her arm and her wrist, affected by a diagnosed condition of reflex sympathetic dystrophy, yielded moderate pain relief.

Example 63

3.6 grams gabapentin was dissolved with 5.4 ml ethoxy diglycol using a mortar and pestle. 9.6 grams ketoprofen and 2.7 grams piroxicam were added and the resultant composition mixed well. 19.8 milliliters soya lecithin was added and resultant mixture mixed well and added to a sufficient quantity of 20% pluronic gel to yield 90 milliliters of a composition having about 10 percent ketoprofen, 4% gabapentin and 3% piroxicam.

Example 64

3.6 grams gabapentin was dissolved with 5.4 ml ethoxy diglycol using a mortar and pestle. 9 grams ketoprofen and 0.9 grams piroxicam were added and mixed well. 19.8 milliliters soya lecithin was added to the resultant mixture and mixed well. Sufficient amount of pluronic gel 20% was added to yield 90 milliliters of a composition having approximately 10% ketoprofen, 4% gabapentin and 1% piroxicam.

Example 65

12 g doxepin was mixed with 50 ml Pluronic F127 33% and placed in a refrigerator to dissolve. 12 g gabapentin was dissolved in 9 ml ethoxy diglycol and mixed to form a smooth paste. 52.8 ml of soya lecithin was added and mixed well. The doxepin/Pluronic mixture was added and mixed well. Sufficient quantity of Pluronic F 127 20% was added to produce 240 ml of a composition having about 5 wt % gabapentin and 5 wt % doxepin.

Example 66

A 36 year old man with a knee injury involving joint surface damage and vascular compromise applied a mixture, prepared generally according to Example 65 to his knee several times per day. He reported moderate to major (40%) relief of pain that persisted for 4 to 6 hours. An earlier trial of carbamazepine-amitriptyline gel produced no relief when applied to his knee.

Example 67

6 gm doxepin was mixed with 18 ml of Pluronic 33% to and placed in a refrigerator to dissolve. 6 gm gabapentin was

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ground in a mortar and pestle to a fine powder, added to 6 ml ethoxy diglycol and mixed to form a smooth paste. 12 gm guaifenesin was added and mixed well. 26.4 ml soya lecithin was added and mixed well. The doxepin/Pluronic mixture was added and mixed well. Sufficient quantity of Pluronic gel (25.2 ml of 33% Pluronic, although 30% or 20% Pluronic can be used), was added to produce 120 ml of a composition having about 5 wt % gabapentin, about 5 wt % doxepin and about 10 wt % guaifenesin.

Example 68

A 55 year old woman with a back and shoulder injury sustained as a nursing care provider applied a mixture, prepared generally according to Example 67, to her back three times per day for a period of two weeks and achieved major relief. She applied the same mixture to her hip and leg and reported moderate to major relief. A mixture containing only doxepin provided only moderate relief to her back, and mild to moderate relief to her hip and leg. A mixture that contained only ketoprofen, gabapentin and piroxicam provided only mild relief to her back.

Example 69

A 59 year old woman with cervical and back strain applied a mixture, prepared generally according to example 51, but without steps involving ketoprofen) containing about 5 wt % doxepin and about 10 wt % guaifenesin, to her neck for a period of two weeks, two to four times per day, and achieved total relief. She applied the same mixture to her back and achieved major to total relief.

Example 70

4.5 gm of doxepin HCl was dissolved using 2.5 ml 95% alcohol and mixed well between syringes. It is also possible to mix the doxepin with 5 ml Pluronic 20% and place in a refrigerator to dissolve. Sufficient quantity of 20% Pluronic F127 was added to produce 90 ml of a composition having about 5 wt % doxepin. Preferably this and other disclosed compositions are protected from light.

Example 71

A 61 year old man with injuries to his back, neck and arm applied a mixture (prepared generally according to Example 70) to his neck four times per day and achieved major relief. He applied the same mixture to his elbow and achieved moderate relief.

Example 72

A formulation of 7% antidepressant and about 10% muscle relaxant was prepared by dissolving 3.15 g of trimipramine and 4.5 g of guaifenesin in a mixer jar using 2.7 mL of ethoxy diglycol. About 9.9 mL of soya lecithin was added and the mixture was mixed well. Sufficient quantity of Pluronic F127 NF (20%) to make total volume of about 45 mL was added and mixed well.

Example 73

A gel formulation of 30% NTHE was prepared from 36 g of celecoxib, 7.2 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (20%) to make total volume of 120 mL.

Example 74

A gel formulation containing about 7% antidepressant and about 13% muscle relaxant was prepared from 14.4 g of

doxepin, 31.2 g of guaifenesin, 12 mL of ethoxy diglycol, 52.8 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 240 mL.

Example 75

A gel formulation containing 5% antiepileptic was prepared from 6 g of lamotrigine, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 76

A gel formulation containing 10% adrenergic agonist was prepared from 12 g of crushed tizanidine, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 77

A gel formulation containing 10% muscle relaxant was prepared from 12 g of crushed metaxalone, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 78

A gel formulation containing 10% muscle relaxant was prepared from 12 g of crushed carisoprodol, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 79

A gel formulation containing 10% methocarbamol was prepared from 12 g of crushed methocarbamol, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 80

A gel formulation containing 10% muscle relaxant was prepared from 12 g of crushed dantrolene sodium, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 81

A gel formulation containing 7% antidepressant, 10% muscle relaxant was prepared from 8.4 g of crushed doxepin, 12 g of chlorzoxazone, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 82

A series of experiments in human subjects were performed using various combinations of pharmaceuticals. The results are indicated in FIG. 2.

Values of pain relief as rated by the patients are provided for each body part for which the medication was administered. The scale used in FIG. 2, is as follows:

0 = None	no benefit or equivocal benefit
1 = Mild	less than 15% pain reduction
1.5 = Mild-moderate	15-25% pain reduction

-continued

2.0 = Moderate	25-33% pain reduction
2.5 = Moderate-major	33-45% pain reduction
3.0 = Major	45-60% pain reduction
3.5 = Major-total	60-80% pain reduction
4.0 = Total	greater than 80% pain reduction

For each body part and for each percentage composition of each compounded medication, the individual ratings as well as a mean, which is the statistical mean of the values given according to the scale listed above, are provided. For example, 3 patients were administered doxepin 5% to their back, and the mean level of relief was 2.333. By contrast, 13 patients received the 5%/10% doxepin-guaifenesin combination, and their mean level of pain relief was 2.885. Results for 7/10 and 10/10 compositions of doxepin guaifenesin are also given, and the mean for the entire sample of dox-guai in all combinations is provided at the end of the section, namely 2.722.

The abbreviations used in FIG. 2 are as follows:

Abbreviations	Generic Pharmaceutical names
c-dox-gu	carbamazepine doxepin guaifenesin
c-gab-do	carbamazepine gabapentin doxepin
carb	carbamazepine
carb-ami	carbamazepine amitriptyline
carb-gab	carbamazepine gabapentin
dox	doxepin
dox-chl	doxepin chlorzoxazone
dox-guai	doxepin guaifenesin
g-dox-gu	gabapentin doxepin guaifenesin
gab-dox	gabapentin doxepin
k-ca-dox	ketoprofen carbamazepine doxepin
k-car-pi	ketoprofen carbamazepine piroxicam
k-dox-ch	ketoprofen doxepin chlorzoxazone
k-dox-gu	ketoprofen doxepin guaifenesin
k-dox-pi	ketoprofen doxepin piroxicam
k-g-do-g	ketoprofen gabapentin doxepin guaifenesin
k-gab	ketoprofen gabapentin
k-gab-ami	ketoprofen gabapentin amitriptyline
k-gab-do	ketoprofen gabapentin doxepin
k-gab-gu	ketoprofen gabapentin guaifenesin
k-gab-pi	ketoprofen gabapentin piroxicam
k-pi	ketoprofen piroxicam
la-li-gu	lamotrigine lidocaine guaifenesin
lam-chl	lamotrigine chlorzoxazone
n-dox-ch	naproxen doxepin chlorzoxazone
naproxen	naproxen
tri-chl	trimipramine chlorzoxazone

Based on the results described herein, doxepin appears to be an effective pain relief medication when administered transdermally and appears to be substantially free of side effects when administered transdermally as described herein.

Doxepin appears to provide about three times the positive response rate compared to at least some other pharmaceutical agents described herein, regardless of whether such other pharmaceutical agents are administered singly or in combination. Doxepin appears to be substantially more effective than amitriptyline as a pain, e.g., neuropathic pain agent when administered transdermally. This appears to be true regardless of whether doxepin is administered as a single agent or is administered in combination with other pharmaceuticals as described herein.

Carbamazepine appears to provide positive effects as a pain, e.g., neuropathic pain agent, at least in properly selected patients. Carbamazepine appears to cause a rash in at least some patients, requiring its discontinuation.

These side effects appear similar to those that are noted for oral administration of carbamazepine. Gabapentin appears to be free of side effects when administered transdermally. Although some patients appear to derive some benefit from a combination of transdermally administered ketoprofen, gabapentin, and prilocain, the effect appears to be relatively weak compared to the effect provided by doxepin.

Guaifenesin appears to provide benefit as an adjunctive treatment, of painful spasticity. For the patient population described herein, amitriptyline appeared to offer limited pain relief when administered transdermally. It appears that combining gabapentin with doxepin may offer some additional benefit. The addition of guaifenesin to doxepin may be of particular value when painful spasticity is present.

In view of the above, the invention provides treatment to patients for whom oral delivery is suboptimal, such as patients who experience gastrointestinal or other side effects, patients who experience poor absorption for orally delivered pharmaceuticals and/or patients who benefit from delivery over an extended period or a relatively rapid delivery or higher rate of increase of plasma levels. The present invention achieves delivery of therapeutic amounts of pharmaceuticals, for at least some patient populations, substantially without skin irritation, gastrointestinal or other side effects associated with orally-delivered pharmaceuticals, especially psychopharmaceuticals, and yields clinical benefits comparable to or greater than those received by patients to whom corresponding pharmaceuticals were administered orally. In view of the above reasons, particularly effective pain medications are those described in examples 65, 67, 69 and 70.

A number of variations and modifications of the invention can also be used. It is believed that blood plasma levels may be increased by providing for two or more transdermal applications per day and/or applying a transdermal composition to two or more sites.

In at least one case, application of a Prozac gel formulation twice daily appeared to approximately double the plasma level. It is believed that an approach such as applying a Prozac gel formulation twice daily to two sites will yield middle range therapeutic levels of about 140-250 ng/ml. At least partially on the basis of the results described herein for fluoxetine, it is believed olanzapine (sold under the trade

name Zyprexa) or a fluoxetine/olanzapine mixture in a lecithin organogel will prove useful.

Other types of psychotropic or psychopharmaceutical medications for which the described transdermal delivery may be used including psychostimulant medications. One example of a psychostimulant medication is Methylphenidate (sold under the trade name Ritalin) used in the treatment of attention deficit hyperactivity disorder (ADHD). Methylphenidate typically has a 2-4 hour duration of action necessitating frequent dosing of a patient which is particularly difficult to accomplish with children in school. It is believed that by using transdermal administration, it will be possible to achieve an extension of effective dosing throughout the day, eliminating the need for frequent oral medication administration. It is believed that transdermal administration will also eliminate peaks and valleys of blood plasma levels which, it is believed, will be more clinically effective. It is believed similar results will be obtained with other pharmaceuticals, for example, Dextroamphetamine (under the trade name Dexedrine) although it is believed the need is less acute since a time release "spansule" form of the medication is available which typically has a 5-6 hour duration of action. Another group of psychotropic medications which, it is believed, will benefit from transdermal delivery includes antipsychotic medication such as those used in the treatment in schizophrenia.

Embodiments of the invention include, but are not necessarily limited to, use by patients with enteric absorption deficits.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

What is claimed is:

1. A transdermal composition for the relief of pain in a subject comprising lamotrigine, doxepin and a muscle relaxant selected from the group consisting of guaifenesin, chlorzoxazone, dantrolene sodium, metaxalone, carisoprodol, and combinations thereof, in lecithin organogel, wherein said pain relief obtainable from the combination of lamotrigine, doxepin and muscle relaxant exceeds the degree of pain relief obtainable from doxepin alone.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

NT NO. : 6,572,880 B2
D : June 3, 2003
INVENTOR(S) : Murdock et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1,

Line 38; replace "groiip" with -- group --.

Signed and Sealed this

Twelfth Day of August, 2003

A handwritten signature in black ink, appearing to read "James E. Rogan", with a horizontal line drawn underneath it.

JAMES E. ROGAN
Director of the United States Patent and Trademark Office



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(54) **METHODS AND TRANSDERMAL
COMPOSITIONS FOR PAIN RELIEF**

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now abandoned, which is a continuation-in-part of
application No. PCT/US99/14653, filed on Jun. 29,
1999 and which is a non-provisional of provisional
application No. 60/122,903, filed on Mar. 5, 1999 and**

**which is a continuation-in-part of application No.
09/106,684, filed on Jun. 29, 1998, which is a con-
tinuation-in-part of application No. PCT/US97/
19651, filed on Oct. 24, 1997. Continuation-in-part of
application No. 08/957,485, filed on Oct. 24, 1997,
now abandoned, which is a non-provisional of pro-
visional application No. 60/029,120, filed on Oct. 24,
1996.**

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(51) **Int. Cl.⁷ A61K 31/551; A61K 9/00**

(52) **U.S. Cl. 424/400; 514/220**

(57) **ABSTRACT**

**The present invention features methods and compositions
for transdermal administration. In one embodiment, the
invention features methods and compositions for transder-
mal administration of an amine containing compound hav-
ing biphasic solubility and/or an agent which enhances the
activity of the amine containing compound having biphasic
solubility, e.g., a muscle relaxant, to relieve pain.**

cpt 90862 Medication Management (cdw ver. 4-24-95)

90862.DOC

Patient: _____ Date _____

Current Medication: 1) _____
 2) _____
 3) _____
 4) _____
 5) _____
 6) _____

Diagnoses: Axis 1: _____
 Axis 2: _____ Axis 3: _____
 GAF _____

Subjective: _____

Objective :	APPEARANCE _____	AFFECT _____
	SPEECH _____	CONCENTRATION _____
	MEMORY _____	IRRITABILITY _____
	APPETITE _____	A/V HALLUC. _____
	CRYING SPELLS _____	ENERGY LEVEL _____
	SLEEP _____	WEIGHT _____

SIDE EFFECTS: _____

RESPONSE OF DEPRESSION SYMPTOMS TO MEDICATIONS:
 EXCELLENT GOOD FAIR POOR N/A

RESPONSE OF ANXIETY SYMPTOMS TO MEDICATIONS:
 EXCELLENT GOOD FAIR POOR N/A

CONCURRENT MEDICATION CONDITIONS: _____

ASSESSMENT: _____

PLAN: 1) Continue meds: _____
 2) Change dosage: _____
 3) New Med: _____
 4) _____

LAB STUDIES ORDERED: _____
 OTHER: _____

Fig. 1

Case Processing Summary(a)

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
ankle * MEDS * Composition	4	3.1%	127	96.9%	131	100.0%
arm * MEDS * Composition	10	7.6%	121	92.4%	131	100.0%
Back * MEDS * Composition	69	52.7%	62	47.3%	131	100.0%
elbow * MEDS * Composition	11	8.4%	120	91.6%	131	100.0%
headache * MEDS * Composition	131	100.0%	0	.0%	131	100.0%
Knee * MEDS * Composition	19	14.5%	112	85.5%	131	100.0%
hip * MEDS * Composition	15	11.5%	116	88.5%	131	100.0%
Neck * MEDS * Composition	28	21.4%	103	78.6%	131	100.0%
leg * MEDS * Composition	13	9.9%	118	90.1%	131	100.0%
shoulder * MEDS * Composition	25	19.1%	106	80.9%	131	100.0%
wrist * MEDS * Composition	26	19.8%	105	80.2%	131	100.0%
a Limited to first 150 cases						

P

				Case Number	ankle	arm
c-dox-gu	Composition	5/5/10	1	26	.	.
			2	33	.	.
			3	41	.	.
			4	59	.	.
			5	73	.	.
			6	80	.	.
		4/5/10	Total	N		
				Mean		
			1	98	.	.
			2	112	.	.
			Total	N		
				Mean		

Fig. 2

		Total	N			
			Mean			
c-gab-do	Composition	5/5/5	1	34	.	.
			Total	N		
				Mean		
		Total	N			
			Mean			
carb	Composition	4	1	5	.	.
			Total	N		
				Mean		
		6	1	81	.	.
			Total	N		
				Mean		
carb-ami	Composition	Total	N			
			Mean			
		4/5	1	12	.	.
			2	40	.	.
			3	49	.	.
			4	64	.	.
carb-gab	Composition	4/4	Total	N		
				Mean		
		Total	1	27	.	mild-moderate
			2	35	.	.
			3	126	.	moderate
			Total	N		2
				Mean		1.750
		Total	N			2
			Mean			1.750
			1	4	.	moderate
			2	13	.	.
			3	15	.	.

Fig. 2 (cont'd)

dox	Composition	5	4	42	.	.
			5	46	.	none
			6	74	.	.
			7	95	moderate	.
			8	116	.	.
			9	121	.	.
			10	128	.	moderate
			Total	N	1	3
				Mean	2.000	1.333
		Total	N		1	3
			Mean		2.000	1.333
dox-chl	Composition	7/13	1	10	.	.
			Total	N		
				Mean		
		5/10	1	21	.	.
			2	29	.	.
			3	30	.	.
			Total	N		
				Mean		
		7/10	1	83	.	.
			Total	N		
				Mean		
		Total	N			
			Mean			
			1	7	.	.
			2	9	.	.
			3	14	.	.
			4	18	.	.
			5	20	.	.
			6	25	.	.
			7	36	.	.
			8	50	.	.

Fig. 2 (cont'd)

dox-guai	Compsition	5/10	9	58	.	.
			10	71	.	.
			11	76	.	.
			12	77	.	.
			13	90	.	.
			14	97	.	.
			15	101	.	.
			16	103	.	.
			17	108	.	.
			18	123	.	.
			19	131	.	.
			Total	N		
				Mean		
		7/10	1	22	.	.
			2	47	.	.
			3	111	.	.
			Total	N		
				Mean		
		10/10	1	23	.	.
			2	48	.	.
			3	53	.	.
			4	57	.	.
			5	67	.	.
			Total	N		
				Mean		
		Total	N			
			Mean			
		4/5/10	1	11	.	.
			Total	N		
				Mean		
			1	1	.	.
			2	32	.	.
			3	39	.	.

Fig. 2 (cont'd)

MEDS	g-dox-gu	Composition	5/5/10	4	44	.	.
				5	51	.	.
				6	54	.	.
				7	62	.	.
				8	72	.	.
				9	85	.	.
				10	87	.	.
				11	93	.	.
				12	119	.	.
				13	129	.	.
				Total	N		
					Mean		
			Total	N			
				Mean			
	gab-dox	Composition	5/5	1	37	.	.
				2	65	.	.
				3	68	.	.
				Total	N		
					Mean		
			Total	N			
				Mean			
	k-ca-dox	Composition	10/4/5	1	86	.	.
				Total	N		
					Mean		
				Total	N		
					Mean		
			10/6/3	1	43	.	.
				Total	N		
					Mean		
				1	102	.	.

Fig. 2 (cont'd)

k-car-pi	Composition	10/4/3	2		104		
			Total	N			
				Mean			
		Total	N				
k-dox-ch	Composition	20/10/5	1		100		
			Total	N			
				Mean			
		Total	N				
k-dox-gu	Composition	3/5/5	1		6		
			Total	N			
		20/5/10	1		63		
			Total	N			
k-dox-pi	Composition	10/4/3/5	1		122		
			Total	N			
		Total	N				
			Mean				
k-g-do-g	Composition	10/4/5/10	1		17		
			Total	N			
		Total	N				
			Mean				
k-gab	Composition	20/4	1		115	none	
			Total	N			1
		Total	Mean				.000
			N				1
			Mean				.000
			1		117		

Fig. 2 (cont'd)

k-gab-am	Composition	20/5/5	Total	N			
				Mean			
k-gab-do	Composition	Total	N				
			Mean				
		20/4/5	1		55		
			Total	N			
		10/5/4		Mean			
			1		99	major	
		10/5/5	Total	N		1	
				Mean		3.000	
		20/5/5	1		113		
			Total	N			
		Total		Mean			
			1		118		
		Total		N		1	
				Mean		3.000	
k-gab-gu	Composition	20/4/4/1	1		94		
			Total	N			
		20/5/5		Mean			
			1		105		
		Total	Total	N			
				Mean			
			1		2		
			2		8	major	
			3		19		
			4		31		
			5		38		
			6		45	none	

Fig. 2 (cont'd)

k-gab-pi	Composition	10/4/3	7	56	.	.
			8	78	.	.
			9	89	.	.
			10	109	.	.
			11	120	.	.
			12	124	.	.
			13	130	.	.
			Total	N		2
				Mean		1.500
		10/4/1	1	16	.	.
			2	28	.	mild
			3	52	.	.
			4	66	.	.
			5	69	.	.
			6	75	moderate	.
			7	82	.	.
			8	84	.	.
			9	88	.	.
			10	91	.	.
			11	96	major	.
			12	125	.	.
			Total	N	2	1
				Mean	2.500	1.000
		10/1/3	1	114	.	.
			Total	N		
		Total	N		2	3
			Mean		2.500	1.333
k-pi	Composition	10/3	1	127	.	.
			Total	N		
		Total	N			
			Mean			
			1	110	.	.

Fig. 2 (cont'd)

la-li-gu	Composition	5/5/10	Total	N						
				Mean						
		Total	N							
Mean										
lam-chl	Composition	7/10	1		3	.	moderate-major			
			Total	N			1			
				Mean			2.500			
		10/10	1		24	.		.		
			2		70	.		.		
			3		106	.		.		
			Total	N						
				Mean						
		Total	N				1			
			Mean				2.500			
		n-dox-ch	Composition	30/5/5	1		79	.		.
					Total	N				
Mean										
Total	N									
	Mean									
naproxen	Composition	30	1		60	.		.		
			Total	N						
		Total	N							
tri-chl	Composition	7/10	1		61	.		.		
			Total	N						
				Mean						
		7/13	1		92	.		.		
			2		107	.		.		
			Total	N						
				Mean						
			Total	N						
		Mean								

Fig. 2 (cont'd)

Total	N		4	10
	Mean		2.500	1.400
June 2 1999 N=131				
a Limited to first 150 cases				

Fig. 2 (cont'd)

METHODS AND TRANSDERMAL COMPOSITIONS FOR PAIN RELIEF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. patent application Ser. No. 09/754,500 filed on Jan. 3, 2001, U.S. patent application Ser. No. 09/342,679 filed on Jun. 29, 1999, PCT Application Serial No. PCT/US99/14653 filed on Jun. 29, 1999, U.S. Provisional Patent Application No. 60/122,903 filed on Mar. 5, 1999, U.S. patent application Ser. No. 09/106,684 filed on Jun. 29, 1998, PCT Application Serial No. PCT/US97/19651 filed on Oct. 24, 1997, U.S. patent application Ser. No. 08/957,485 filed on Oct. 24, 1997, and U.S. Provisional Patent Application Serial No. 60/029,120 filed on Oct. 24, 1996, incorporated herein in their entirety by this reference.

FIELD OF THE INVENTION

[0002] The present invention is directed to methods and compositions for transdermal administration. In particular, the present invention is directed to methods and compositions for the transdermal administration of an amine containing compound having biphasic solubility and/or an agent which enhances the activity of the amine containing compound having biphasic solubility, e.g., a muscle relaxant, to relieve pain.

BACKGROUND OF THE INVENTION

[0003] It is believed that damage to somatic sensory nerves causes a somatic sensory loss. Such damage can be caused by a variety of means including trauma, diseases such as diabetes, herpes zoster and late-stage cancer, chemotherapy, or by a chemical injury. It is believed that neural pain circuits rewire themselves, both anatomically and biochemically, after nerve injury. In many patients suffering from damage to somatic sensory nerves, negative symptoms such as numbness are joined by positive sensations, involving a sort of false sensation of pain. The experience can range from mild dysesthesia to excruciating pain, rendering some patients unable to work, walk or do other daily activities.

[0004] In the past, patients were generally treated by administration of analgesics to relieve pain. A vast majority of such patients receive doses of these agents orally. Unfortunately, in some situations, oral administration of such agents has been associated with a variety of side effects, such as liver damage, kidney damage, gastrointestinal side effects, addiction, sedation, and/or weight gain which cannot be tolerated well by the patient. In other cases, malabsorption of oral preparations have resulted in subtherapeutic plasma levels. In other cases, the agents have relatively short plasma half-lives, necessitating inconveniently frequent dosing. In general, oral delivery involves a time delay as the analgesic is absorbed via the digestive system before entering the bloodstream. A number of agents which have traditionally been administered orally or by injection have been inappropriate or suboptimal for some patients when so-administered. There are a number of medications which, in at least some patients, are not tolerated well when orally administered (e.g. which cause undesirable gastrointestinal or other side effects) and/or which provide undesirably high

or low concentrations or delayed concentrations in a target tissue. In some cases, dosages which are appropriate for oral administration, upon being distributed more or less uniformly throughout the body, are undesirably low in a particular area, e.g., tissue, to achieve desired results. Oral or injection administration may result in too slow or too rapid increase in blood plasma levels, e.g., may involve an undesirably long time delay as the analgesic is absorbed by the digestive system before entering the bloodstream, or may result in a "spike" in blood plasma levels followed by an undesirably low level, where a more constant level would be preferable. Some analgesics are particularly prone to cause or contribute to kidney or liver damage when administered orally.

[0005] Although other forms of delivery of pharmaceuticals agents are known, each has its drawbacks. Parenteral (i.e., intravenously or intramuscularly injected) administration is inconvenient and expensive, and is rarely used outside the hospital. Inhalation is believed to be not feasible with many analgesic agents currently in use. Therefore, there is a need for an analgesic delivery system which provides effective and acceptable levels, while preferably avoiding or reducing undesired effects such as liver damage or gastrointestinal side effects.

SUMMARY OF THE INVENTION

[0006] The present invention provides a transdermal composition for the treatment of pain in a subject, particularly a human subject. The transdermal composition for the treatment of pain in a subject includes an amine containing compound having biphasic solubility in an amount effective to treat pain in a subject and a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound, e.g., a lecithin organogel carrier. In a preferred embodiment, the transdermal composition further includes an agent which enhances the activity of the amine containing compound having biphasic solubility, e.g., a muscle relaxant, such as guaifenesin, chlorzoxazone, dantrolene sodium, metaxalone, carisoprodol, and combinations thereof. Preferably, the agent which enhances the activity of the amine containing compound having biphasic solubility, e.g., the muscle relaxant, also has a biphasic solubility.

[0007] In one embodiment of the present invention, the amine containing compound having biphasic solubility is an antidepressant compound, such as a tricyclic antidepressant compound, e.g., doxepin or trimipramine.

[0008] In another embodiment of the present invention, the amine containing compound having biphasic solubility is a sodium channel blocker, a calcium channel blocker, an anti-epileptic compound, or an anti-convulsant compound.

[0009] Another embodiment of the invention features a transdermal composition which includes an amine-containing compound as described herein and an anti-inflammatory compound, such as a nonsteroidal anti-inflammatory compound, e.g., celecoxib, etodolac, mefenamic acid, nabumetone, salsalate, naproxen, viox®[®], and combinations thereof. Such a composition can further include an agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant such as guaifenesin.

[0010] In another aspect, the invention features a transdermal composition for the treatment of pain in a subject

including an amine containing compound having biphasic solubility in an amount effective to treat pain in a subject; a muscle relaxant in an amount effective to enhance the activity of the amine containing compound having biphasic solubility; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound having biphasic solubility and the muscle relaxant.

[0011] In yet another aspect, the invention features a transdermal composition for the treatment of pain in a subject including doxepin in an amount effective to treat pain in a subject; guaifenesin in an amount effective to enhance the activity of doxepin; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the doxepin and the guaifenesin.

[0012] Other aspects of the invention feature methods for treating pain in a subject in which the subject is contacted with a transdermal composition including an amine containing compound having biphasic solubility in an amount effective to treat pain in the subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound to thereby treat pain in the subject. In a preferred embodiment, the transdermal composition is applied to the skin of the subject.

[0013] Another aspect of the invention features a method for selecting a compound suitable for treating pain in a subject. The method includes transdermally administering an amine containing compound having biphasic solubility to a subject; and determining whether pain is treated in the subject to thereby select a compound suitable for treating pain in a subject. In a preferred embodiment, the method can further include modeling the compound using a computer equipped with a three-dimensional chemical structure modeling program; and determining whether the three-dimensional chemical structure of the compound possesses sufficient characteristics to be useful as a sodium channel blocker or a calcium channel blocker, thereby selecting a compound suitable for treating pain in a subject.

[0014] In another aspect, the invention features a transdermal composition suitable for transdermal delivery, which includes a therapeutically effective amount of a pharmaceutical compound (e.g., a serotonin specific reuptake inhibitor, a mood stabilizing compound, a dopamine compound, a compound suitable for treating attention deficit hyperactivity disorder, a compound suitable for treating hypertension and akathisia, an analgesic compound, or a compound used in the treatment of impotence) and a pharmaceutically acceptable carrier suitable for transdermal delivery of the pharmaceutical compound, e.g., a lecithin organogel carrier.

[0015] In yet another aspect, the invention features a transdermal composition for treatment of pain in a subject which includes a compound capable of blocking afferent neuron transmission in an amount effective to block afferent neuron transmission in a subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the compound.

[0016] In a further aspect, the present invention features transdermal compositions comprising lamotrigine and doxepin; topiramate and chlorzoxazone; topiramate and guaifenesin; topiramate and doxepin; topiramate and naproxen; doxepin and chlorzoxazone; lamotrigine and guaifenesin; lamotrigine, doxepin, and guaifenesin; or lamotrigine, doxepin, and chlorzoxazone.

[0017] In another aspect, the present invention provides a transdermal composition comprising a muscle relaxant and a pharmaceutically acceptable carrier suitable for transdermal delivery of the muscle relaxant to a subject. Preferably, the muscle relaxant is present in the transdermal composition in an amount effective to treat pain, e.g., localized pain. For example, the muscle relaxant may constitute from about 1% by weight (% by wt.) to about 30% by wt. of the total amount of the composition, more preferably from about 3% by wt. to about 15% by wt., and most preferably from about 5% by wt. to about 13% by wt. Moreover, ranges of values using a combination of any of the above recited values as upper and/or lower limits are intended to be included.

[0018] In one embodiment the muscle relaxant is selected from the group consisting of guaifenesin, chlorzoxazone, benzodiazepines such as clozapine and diazepam, dantrolene sodium, metaxalone, carisoprodol, and combinations thereof. The muscle relaxant is, preferably, chlorzoxazone and, more preferably, guaifenesin.

[0019] In another aspect, the present invention provides a method for treating pain in a subject in which the subject is contacted with a transdermal composition including a muscle relaxant in an amount effective to treat pain in the subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the muscle relaxant to thereby treat pain (e.g., localized pain) in the subject. In a preferred embodiment, the transdermal composition is applied to the skin of the subject.

[0020] Other features and advantages of the invention will be apparent from the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] FIG. 1 is an evaluation form used in evaluating an embodiment of the present invention.

[0022] FIG. 2 is a table depicting the results from clinical experiments using compositions of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0023] The present invention provides a transdermal composition suitable for treatment of pain in a subject. The transdermal composition includes an amine containing compound having biphasic solubility in an amount effective to treat pain in a subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound having biphasic solubility.

[0024] As used herein, the term "subject" includes a mammal, such as a human, a horse, a pig, a cow, a mouse, a rat, a rabbit, or a goat. In preferred embodiment, the subject is a human.

[0025] As used herein, the term "pain" is art recognized and includes a bodily sensation elicited by noxious chemical, mechanical, or thermal stimuli, in a subject, e.g., a mammal such as a human. The term "pain" includes chronic pain, such as lower back pain; pain due to arthritis, e.g., osteoarthritis; joint pain, e.g., knee pain or carpal tunnel syndrome; myofascial pain, and neuropathic pain. The term "pain" further includes acute pain, such as pain associated with muscle strains and sprains; tooth pain; headaches; pain

associated with surgery; or pain associated with various forms of tissue injury, e.g., inflammation, infection, and ischemia.

[0026] As used herein, the term "amine containing compound having biphasic solubility" includes compounds having at least one amine moiety and having sufficient lipid solubility (e.g., solubility in polar solvents such as ethanol, ethoxydiglycerol, ethoxydiglycol, chloroform, benzene, and the like) such that the compound passes through the stratum corneum, and has sufficient aqueous solubility to be active in the aqueous environment of the dermis and the underlying tissue.

[0027] Transdermal compositions of the present invention include an amine containing compound having biphasic solubility in an amount effective to treat pain in a subject. As used herein, the terms "amount effective to treat pain in a subject" and "effective amount" are used interchangeably herein and include an amount effective, at dosages and for periods of time necessary, to achieve the desired result, e.g., sufficient to treat pain in a subject. An effective amount of an amine containing compound or a pharmaceutical compound as defined herein may vary according to factors such as the disease state, age, and weight of the subject, and the ability of the amine containing compound or pharmaceutical compound to elicit a desired response in the subject. Dosage regimens may be adjusted to provide the optimum therapeutic response. An effective amount is also one in which any toxic or detrimental effects of the amine containing compound having biphasic solubility or pharmaceutical compound are outweighed by the therapeutically beneficial effects.

[0028] The transdermal compositions of the invention can further include an agent which enhances the activity of the amine containing compound having biphasic solubility. As used herein, an "agent which enhances the activity of the amine containing compound having biphasic solubility" includes an agent which enhances the pharmacological activity of the amine containing compound having biphasic solubility (e.g., the ability of the amine containing compound to treat pain), or enhances the transdermal delivery of the amine containing compound having biphasic solubility (e.g., the ability of the amine containing compound to cross the stratum corneum), or enhances both the pharmacological activity and the transdermal delivery of the amine containing compound. Examples of agents which enhance the activity of the amine containing compound having biphasic solubility, include muscle relaxants, described in further detail below.

[0029] As used herein, the term "transdermal" composition includes compositions capable of passing through the stratum corneum of a subject. The term transdermal further includes compositions capable of passing through the epidermis of a subject, compositions capable of passing through the dermis of a subject, and compositions capable of passing through the hypodermis of a subject. In preferred embodiments, the term transdermal includes compositions capable of passing through the skin of a subject and reaching the underlying tissues and organs.

[0030] As used herein, the term "transdermal delivery" includes delivery of, for example, a compound through the stratum corneum of a subject. The term transdermal delivery further includes delivery of, for example, a compound

through the epidermis of a subject, delivery of, for example, a compound through the dermis of a subject, and delivery of, for example, a compound through the hypodermis of a subject. In preferred embodiments, the term transdermal delivery includes delivery of, for example, a compound through the skin of a subject to the underlying tissues and organs.

[0031] The present invention further features a transdermal composition for treatment of pain in a subject which includes a compound capable of blocking afferent neuron transmission in an amount effective to block afferent neuron transmission in a subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the compound.

[0032] As used herein, the term "compound capable of blocking afferent neuron transmission" includes a compound which is capable of blocking the ability of an afferent neuron, i.e., a sensory neuron, to carry an impulse toward the central nervous system.

[0033] Various aspects of the invention are described in further detail in the following subsections:

Amine Containing Compounds having Biphasic Solubility

[0034] Amine containing compounds having biphasic solubility for use in the transdermal compositions of the invention include antidepressant compounds, antiepileptic compounds, anticonvulsant compounds, sodium channel blockers and calcium channel blockers.

[0035] As used herein, the term "antidepressant compounds" includes compounds capable of alleviating the symptoms of depression. Examples of antidepressant compounds include all tricyclic antidepressants (e.g., amitriptyline, dothiepin, or lofepramine), bupropion (sold under the trade name Wellbutrin), reboxetine (sold under the trade name Edronax), nefazodone (sold under the trade name Serzone) and trazodone (sold under the trade name Desyre). Antidepressant compounds are described in, for example, the 1998 SIGMA catalogue and the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, the contents of which are incorporated herein by reference.

[0036] In one embodiment of the present invention, the antidepressant compounds of the present invention contain a tricyclic moiety. Therefore, in a preferred embodiment, a transdermal composition of the present invention includes a tricyclic antidepressant compounds. Exemplary tricyclic antidepressants include adinazolam, amitriptylinoxide, amoxapine, clomipramine, demexiptiline, dimetacrine, dothiepin, doxepin, imipramine N-oxide, iprindole, lofepramine, melitracen, metapramine, noxiptilin, pizotiline, propizepine, quinupramine, tianeptine, and trimipramine. A particularly preferred tricyclic antidepressant for use in the compositions of the invention is doxepin.

[0037] Tricyclic antidepressant compounds are described in, for example, "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995), the contents of which are incorporated herein by reference.

[0038] Preferably, the tricyclic antidepressant compound is selected from the group consisting of doxepin, trimipramine, other tricyclics having biphasic solubility, and

combinations thereof. When combined with other compounds, such as an agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant, and/or an anti-inflammatory compound, e.g., a nonsteroidal anti-inflammatory compound, as discussed below, the tricyclic antidepressant preferably constitutes from about 1% by weight (% by wt.) to about 30% by wt. of the total amount of the pharmaceutical, more preferably from about 3% by wt. to about 15% by wt., and most preferably from about 5% by wt. to about 13% by wt.

[0039] The amine containing compounds having biphasic solubility used in the transdermal compositions of the invention further include antiepileptic compounds. As used herein, the term "antiepileptic compound" includes compounds capable of alleviating the symptoms of epilepsy. Exemplary antiepileptic compounds for use in the compounds of the invention include lamotrigine, felbamate, and carbamazepine. Preferably, the antiepileptic compound is selected from the group consisting of lamotrigine, felbamate, carbamazepine, and combinations thereof. When combined with other compounds, such as an agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant, and/or an anti-inflammatory compound, e.g., a nonsteroidal anti-inflammatory compound as discussed below, the antiepileptic compound constitutes from about 1% by wt. to about 30% by wt. of the total amount of the pharmaceutical, more preferably from about 3% by wt. to about 20% by wt., and most preferably from about 5% by wt. to about 15% by wt. Antiepileptic compounds are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, and the "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995) the contents of which are incorporated herein by reference.

[0040] In another aspect of the present invention, the amine containing compounds having biphasic solubility of the present invention include anticonvulsant compounds. As used herein, the term "anticonvulsant compound" includes compounds capable of alleviating the symptoms of convulsion, i.e., the violent involuntary tetanic contractions of an entire group of muscles. Exemplary anticonvulsant compounds which for use in the compositions of the invention include felbamate, lamotrigine and carbamazepine. Preferably, the anticonvulsant compound is selected from the group consisting of felbamate, lamotrigine, and combinations thereof. When combined with other compounds, such as an agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant, and/or an anti-inflammatory compound, e.g., a nonsteroidal anti-inflammatory compound as discussed below, the anticonvulsant compound constitutes from about 1% by wt. to about 30% by wt. of the total amount of the pharmaceutical, more preferably from about 3% by wt. to about 20% by wt., and most preferably from about 5% by wt. to about 15% by wt. Anticonvulsant compounds are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, and the "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995) the contents of which are incorporated herein by reference.

[0041] In yet another aspect of the present invention, the amine containing compounds having biphasic solubility of

the present invention include adrenergic agonist compounds. Preferably, the adrenergic agonist compound is tizanidine. When combined with other compounds, such as a muscle relaxant and/or nonsteroidal anti-inflammatory compound as discussed below, the adrenergic agonist compound constitutes from about 1% by wt. to about 30% by wt. of the total amount of the pharmaceutical, more preferably from about 3% by wt. to about 20% by wt., and most preferably from about 5% by wt. to about 15% by wt. Adrenergic agonist compounds are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, and the "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995) the contents of which are incorporated herein by reference.

[0042] The amine containing compounds having biphasic solubility used in the transdermal compositions of the invention further include sodium channel blockers and calcium channel blockers. As used herein, the term "sodium channel blockers" includes compounds which are capable of blocking the activity of a sodium channel. Examples of sodium channel blockers include topiramate, tetrodotoxin, flecainide, disopyramide, and terfenadine. Sodium channel blockers are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, and the "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995) the contents of which are incorporated herein by reference. As used herein, the term "calcium channel blockers" includes compounds which are capable of blocking the activity of a calcium channel. Examples of calcium channel blockers include Arylalkylamines, e.g., Bepridil, Clentiazem, Diltiazem, Fendiline, Gallopamil, Mibefradil, Prenylamine, Semotiadil, Terodiline, or Verapamil; Dihydropyridine Derivatives, e.g., Amlodipine, Aranidipine, Bamidipine, Benidipine, Cilnidipine, Bfonidipine, Elgodipine, Felodipine, Isradipine, Lacidipine, Lercanidipine, Manidipine, Nicardipine, Nifedipine, Nilvadipine, Nimodipine, Nisoldipine, or Nirrendipine; Piperazine Derivatives, e.g., Cinnarizine, Flunarizine, Lidoflazine, or Lomerizine; Bencyclane; Etafenone; Fantofarone; or Perhexiline.

[0043] Whenever nerves are damaged, for example, by trauma, by diseases such as diabetes, herpes zoster, or late-stage cancer, or by chemical injury (e.g., as an untoward consequence of agents including the false-nucleoside anti-HIV pharmaceuticals), neural pain circuits rewire themselves, anatomically and/or biochemically. Thus, following an injury, new sodium and calcium channels are formed which are believed to constitute the basis for chronic pain development. Through a similar action in the dorsal root ganglia, chronic regional pain syndromes may develop. Each time one of these sodium and/or calcium channels depolarizes, a nerve impulse originates. Because there are so many sodium and calcium channels, there may be a constant cascade of nerve impulses, causing allodynia, burning sensations, and/or dysesthesias. It is believed that some chronic pains may be mediated through sodium and/or calcium channels in nerve cells. Thus, it is believed that amine containing compounds having biphasic solubility which can block sodium and/or calcium channels may also be used in the transdermal compositions of the invention.

[0044] In one embodiment of the invention, the amine moiety of the amine containing compounds having biphasic

solubility of the present invention may function similar to a sodium or calcium ion upon entry into the sodium channel of a nerve cell membrane. A non-polar moiety, which is preferably present in the amine containing compound having biphasic solubility of the present invention may interact with the nerve cell membrane, perhaps through Van der Waals forces. In such cases, it is believed that the presence of the non-polar moiety prevents or inhibits a complete uptake of the amine containing compound having biphasic solubility through the nerve cell membrane. It is believed that one or more these interactions prevent or reduce the amount and/or the rate of depolarization and ion exchange involved in stimulus conduction, thereby decreasing pain sensation.

[0045] The amount of an amine containing compound having biphasic solubility useful in relieving pain transdermally may be determined by methods known in the art, and typically ranges from about 1 mg to about 300 mg per subject per dose, preferably from about 5 mg to about 100 mg per subject per dose, and more preferably from about 10 mg to about 50 mg per subject per dose, depending on a variety of factors including the particular amine containing compound having biphasic solubility used, whether the area of transdermal application is the site of action, and the intended size of the site of action. In a preferred embodiment, the amount of an amine containing compound having biphasic solubility useful in relieving pain transdermally, is 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 mg, 150 mg, 200 mg, 250 mg, or 300 mg per subject per dose.

Muscle Relaxants

[0046] Transdermal compositions of the present invention may also include a muscle relaxant. As used herein, the term "muscle relaxant" includes compounds which facilitate or enhance the relaxation of muscles (e.g., provide relief from muscle spasm) and, thus, facilitate or enhance the transdermal delivery of the transdermal compositions of the invention. Exemplary muscle relaxants include both skeletal muscle relaxants and smooth muscle relaxants such as anticholinergics, antispasmodics, bronchodilators, and vasodilators. Muscle relaxants are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, pp. THER-1 to THER-28, and the "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995) the contents of which are incorporated herein by reference. Preferably, the muscle relaxant is selected from the group consisting of guaifenesin, benzodiazepines (e.g., clonazepam or diazepam), chlorzoxazone, dantrolene sodium, metaxalone, carisoprodol, other muscle relaxants having biphasic solubility, and combinations thereof. More preferably, the muscle relaxant is selected from the group consisting of guaifenesin, chlorzoxazone, and combinations thereof. A preferred muscle relaxant for use in the compositions of the invention is guaifenesin.

[0047] Preferably the muscle relaxant has biphasic solubility. Preferably the muscle relaxant, when present in the pharmaceutical composition, constitutes from about 1% by wt. to about 30% by wt. of the total amount of the pharmaceutical, more preferably from about 3% by wt. to about 20% by wt., and most preferably from about 5% by wt. to about 15% by wt.

Anti-inflammatory Compounds

[0048] The transdermal compositions of the present invention may also include an anti-inflammatory compound. As used herein, the term "anti-inflammatory compound" includes a compound which is capable of reducing cell migration, caused by ischemic and trauma associated events, and therefore reduces edema formation to thereby provide pain relief. Preferably, the anti-inflammatory compound is a nonsteroidal anti-inflammatory compound (i. e., NTHE) including ketoprofen. Anti-inflammatory compounds, e.g., NTHEs, are described in, for example, the 1998 SIGMA catalogue, the "The Merck Index", 12th Ed., Budavari et al., eds., Merck & Co., Inc., Rahway, N.J., 1996, pp. THER-1 to THER-28, and the "Guide to Clinical Neurology" by J. P. Mohr et al. (Churchill Livingstone, 1995) the contents of which are incorporated herein by reference. Preferably, the NTHE is selected from the group consisting of celecoxib, etodolac, mefenamic acid, nabumetone, salsalate, naproxen, Vioxx®, COX-2 NTHEs having biphasic solubility, and combinations thereof.

[0049] More preferably, the NTHE is selected from the group consisting of celecoxib, etodolac, naproxen, COX-2 NTHEs having biphasic solubility, and combinations thereof. Preferably, the NTHE has biphasic solubility. The NTHE, when present in the transdermal composition, preferably, constitutes from about 1% by wt. to about 30% by wt. of the total amount of the pharmaceutical, more preferably from about 3% by wt. to about 30% by wt., and most preferably from about 5% by wt. to about 30% by wt.

Dosages

[0050] The concentration as well as the quantity of the amine containing compounds having biphasic solubility, the agents which enhance the activity of the amine containing compounds, e.g., the muscle relaxants, and the anti-inflammatory compounds can be varied independently in order to achieve the desired effect. For example, higher concentrations of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds contained in a dosage form of decreased viscosity may result in an analgesic with fast onset and short duration. High concentrations of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds contained in a dosage form of increased viscosity may result in potent analgesic with fast onset and long duration. Low concentrations of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds in a dosage form of decreased viscosity may result in mild analgesic with longer onset and short duration. Low concentrations of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds contained in a dosage form of increased viscosity may have mild analgesic properties with longer onset and longer duration. The ability to vary the concentration of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds from very low to high of the total composition, combined with the ability to coat thin (about 0.1 mm) or thick (about 0.5 mm) enables the practitioner of the invention to vary the dosage of the system as needed for particular level of pain and anatomical sites of interest. It should be appreciated, however, that onset time as well as

duration of analgesic effect of the transdermal composition of the present invention will vary from subject to subject as well as on the basis of the site of application, and properties of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds.

[0051] Generally, the concentration of the amine containing compounds having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds can range, on a weight basis, from about 1% to about 30% of the total composition, preferably from about 3% to about 20%, and more preferably from about 5% to about 15%.

Pharmaceutically Acceptable Carriers

[0052] The transdermal compositions of the present invention also includes a pharmaceutically acceptable carrier which is capable of transdermal delivery of the amine containing compound having biphasic solubility. As used herein, the term "pharmaceutically acceptable carrier suitable for transdermal delivery" includes a carrier capable of delivering the amine containing compound transdermally as defined above. Suitable carriers for transdermal delivery of pharmaceuticals are described in U.S. Pat. No. 5,446,070, the contents of which are incorporated herein by reference. Briefly, pharmaceutically acceptable carriers of the present invention include any suitable finite (i.e., solid) or non-finite (i.e., non-solid, such as liquid or semi-liquid) carrier including liquids, semi-liquids or solid carriers, such as a bioadhesive. Thus, the amine containing compounds having biphasic solubility may be admixed with a pharmaceutically acceptable carrier such as a cream, gel, emulsion, lotion, salve, paste, plaster, ointment, spray solution, or any other "non-finite" carrier known in the art of pharmaceutical delivery. For example, the base of a non-finite carrier may be lipid including phospholipids such as lecithins; fatty oils; lanolin; vasoline; paraffins; glycols; higher fatty acids; and higher alcohols.

[0053] The term "bioadhesive" as used herein includes an adhesive which attaches to a biological surface such as skin or mucosal tissue. Preferably, the bioadhesive of the present invention is self-adhesive in that it attaches to the site of interest without the need to reinforce its attachment by way of another adhesive. Suitable bioadhesive include natural or synthetic polysaccharides such as cellulose derivatives including methylcellulose, cellulose acetate, carboxymethylcellulose, hydroxyethylcellulose and the like; pectin; a mixture of sulfated sucrose and aluminum hydroxide; hydrophilic polysaccharide gums including natural plant exudates, such as karaya gum, ghatti gum, tragacanth gum, xanthan gum, jaraya gum and the like; seed gums including guar gum, locust bean gum, psillium seed gum and the like; and lecithins such as soya lecithin. In addition to the above ingredients, compositions of the present invention may also include other ingredients such as various pharmaceutically acceptable additives available to those skilled in the art. These additives include binders, stabilizers, preservatives, flavorings, fragrances, and pigments.

[0054] In another embodiment, the pharmaceutically acceptable carrier of the present invention includes van pen cream (cetyl alcohol, stearyl alcohol, steric acid, glycerol monostearate, isopropyl myristate, soya lecithin, BHT alcohol 95%, simethicone, sodium hydroxide 30% solution, polyoxyl stearate, edetate disodium 5%, purified water, urea).

Other Pharmaceutical Compounds

[0055] In another aspect, the invention features a transdermal composition suitable for transdermal delivery, which includes a therapeutically effective amount of a pharmaceutical compound (e.g., a serotonin specific reuptake inhibitor, a mood stabilizing compound, a dopamine compound, a compound suitable for treating attention deficit hyperactivity disorder, a compound suitable for treating hypertension and akathisia, an analgesic compound, or a compound used in the treatment of impotence) and a pharmaceutically acceptable carrier suitable for transdermal delivery of the pharmaceutical compound.

[0056] As used herein, the term "pharmaceutical compound" includes compounds suitable for treating a targeted condition and capable of being delivered in active form, in vivo. Examples of pharmaceuticals include drugs, enzymes, chemical compounds, combinations of chemical compounds, biological macromolecules and analogs thereof. Examples of pharmaceutical compounds are described in detail below.

[0057] In one embodiment of the invention, the pharmaceutical compound is a serotonin specific reuptake inhibitor (SSRI). SSRIs are commonly prescribed for patients with diagnoses of mood disorders, some forms of anxiety disorder (particularly panic disorder), obsessive compulsive disorders, some forms of menopausal disorders, and eating disorders (especially bulimia nervosa). Examples of such SSRIs include sertraline (sold under the trade name Zoloft), paroxetine (sold under the trade name Paxil), fluoxetine (sold under the trade name Prozac), venlafaxine (sold under the trade name Effexor), and fluvoxamine (sold under the trade name Luvox).

[0058] In another embodiment of the invention, the pharmaceutical compound is a mood stabilizing medication, such as carbamazepine (sold under the trade name Tegretol) and valproic acid (sold under the trade name Depakote). These agents are used frequently in psychiatric practice as either augmentation medications (to render antidepressants more effective) or as anti-manic medications in the treatment of bipolar mood disorder. Mood stabilizing medications are also used in neurologic practice for the treatment of seizure disorders and for the treatment of certain pain disorders.

[0059] In yet another embodiment of the invention, the pharmaceutical compound is a compound used for treating Attention Deficit Hyperactivity Disorder (ADHD), one example of which is permoline, sold under the trade name Cylert. Permoline is a medication that is used in the treatment of Attention Deficit Hyperactivity Disorder in children and adults. It is practically insoluble in water, but soluble in ethylene glycol and lipids, making it a good candidate for transdermal administration.

[0060] In a further embodiment of the invention, the pharmaceutical compound is a dopamine compound, used for treating Parkinson's disease, examples of which are pergolide, sold under the trade name Permax and bromocriptine mesylate, sold under the trade name Parlodel.

[0061] In yet another embodiment of the invention, the pharmaceutical compound is a compound used for treating hypertension and akathisia, one example of which is propranolol, sold under the trade name Inderal.

[0062] In yet a further embodiment of the invention, the pharmaceutical compound is a compound used in the treatment of impotence such as sildenafil, sold under the trade-name Viagra. It is believed that transdermal administration of sildenafil may be useful, for at least some subjects, as compared to oral administration which has been found, in at least some situations, to be associated with gastrointestinal side effects.

Methods for Preparing the Transdermal Compositions

[0063] Another embodiment of the present invention provides a method for preparing the above described transdermal compositions, by admixing a therapeutically effective amount of the amine containing compound having biphasic solubility, optimally an agent which enhances the activity of the amine containing compound, e.g., a muscle relaxant, optimally an anti-inflammatory compound with the carrier suitable for transdermal delivery of the amine containing compound.

[0064] In one embodiment of the present invention, a transdermal composition is prepared by dispersing or dissolving crushed tablets, capsules or other preparation(s) of the amine containing compound having biphasic solubility, the muscle relaxants, and the anti-inflammatory compounds, which were intended for oral delivery, in a gel formed of soya lecithin and isopropyl palmitate or isopropyl myristate, alcohol, or ethoxy diglycol. In another embodiment of the present invention, Pluronic gel, formed of Pluronic such as Pluronic F127, potassium sorbate and water is used.

[0065] In a particular embodiment of the present invention, a transdermal composition including a combination of doxepin with guaifenesin is useful for treating pain. It is believed that transdermal administration of such combination can be advantageous, for at least some patients, as compared to oral administration, because higher local pharmaceutical concentrations at the site(s), e.g., of injury, can be achieved yielding an improved therapeutic response without systemic side effects such as weight gain, drowsiness, gastrointestinal upset and/or other known side effects of these pharmaceuticals.

Methods for Use

[0066] In one embodiment, the invention feature methods for treating pain in a subject in which the subject is contacted with a transdermal composition including an amine containing compound having biphasic solubility in an amount effective to treat pain in the subject; and a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound to thereby treat pain in the subject. In a preferred embodiment, the transdermal composition is applied to the skin of the subject as often as needed for the alleviation of pain. For example, the transdermal composition may be applied daily, weekly, monthly, yearly, for a length of time sufficient to alleviate pain.

[0067] Detailed examples of the preparation are provided below, along with examples of results obtained from transdermal administration to human patients. Preferably, a gel preparation is applied to the skin at the site or sites of pain. Patients can be evaluated by means of a structured evaluation form, e.g., completed at a frequency of at least one time per week. Evaluation of patients are for the present symp-

toms as well as any side effects from currently administered medications. This makes it possible to note changes on an ongoing basis.

[0068] Compositions of the invention can be self-administered doses in the form of a gel applied to the skin by the patient, or be implemented by providing a transdermal preparation in premeasured doses preferably in connection with an adhesive or other covering or patch so that the dosage may be administered e.g., by placing the adhesive patch on the skin of the patient. Although some embodiments of the invention have been described in connection with positioning the pharmaceutical gel on the arm of a patient, other positioning on the skin of a patient can also be used. Because, depending on the formulation, speed or duration of transdermal delivery may vary as function of skin location, in one embodiment the location of the skin to which the pharmaceutical is applied is selected so as to relatively increase or decrease the delay, speed, duration, or rate of delivery of the pharmaceutical, either with respect to a particular tissue or systemically.

[0069] For example, when a rapid rise in blood serum levels is desired, a placement which enhances delivery rate, such as behind the ear, can be used. When it is desired to enhance dose or delivery rate locally, the transdermal formulation may be positioned adjacent the desired treatment area. Membranes or matrices, such as a polymer matrix, may be used to limit or control delivery rates. In addition to transdermal gel or patch delivery, delivery of the transdermal or aerosol formulation can be achieved, e.g. by administration as nose drops, eardrops, eyedrops and/or suppositories.

[0070] In one embodiment, medications dispensed in transdermal gel form will be dispensed in unit doses, such as blister packs. The gel will be extruded from the blister pack, and rubbed on the administration site. The dosage will be adjusted by varying the number of unit dose applied. This will ensure accurate dosimetry and will avoid contamination of the gel.

Methods for Selecting a Compound Suitable for Treating Pain

[0071] In a further aspect, the invention features a method for selecting a compound suitable for treating pain in a subject. The method includes transdermally administering an amine containing compound having biphasic solubility to a subject; and determining whether pain is treated in the subject to thereby select a compound suitable for treating pain in a subject. In a preferred embodiment, the method can further include modeling the compound using a computer equipped with a three-dimensional chemical structure modeling program (e.g., Molecules-3D Professional Edition, version 2.60, copyright 1991-1998, Molecular Arts Corp., © 1994-1998 WCB/McGraw Hill); and determining whether the three-dimensional chemical structure of the compound possesses sufficient characteristics to be useful as a sodium or a calcium channel blocker, thereby selecting a compound suitable for treating pain in a subject.

[0072] The effectiveness of the amine containing compound having biphasic solubility to treat pain can be tested in-vitro or in vivo. An animal model for pain, e.g, such as the one described in Kral M. G. et al. (1999) *Pain* 81(1-2):15-24 can, for example, be used for testing such compounds.

Preferred Transdermal Compositions

[0073] In certain preferred embodiments, the transdermal compositions of the present invention include lamotrigine and doxepin; topiramate and chlorzoxazone; topiramate and guaifenesin; topiramate and doxepin; topiramate and naproxen; doxepin and chlorzoxazone; lamotrigine and guaifenesin; lamotrigine, doxepin, and guaifenesin; lamotrigine, doxepin, and chlorzoxazone; doxepin alone; or guaifenesin alone.

[0074] This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application, as well as the Figures are incorporated herein by reference.

EXAMPLES

Example 1

[0075] One hundred grams of lecithin soya (granular) and 0.66 grams sorbic acid (NF-FCC powder) were dispersed in 100 grams (117 milliliters (mL)) of isopropyl palmitate NF and allowed to stand overnight. Approximately 220 milliliters of lecithin-isopropyl palmitate in a form of a liquid of a syrup consistency was formed.

Example 2

[0076] One hundred grams of lecithin soya (granular) and 0.66 grams sorbic acid (NF-FCC powder) is dispersed in 100 grams (117 milliliters) of isopropyl myristate NF, and allowed to stand overnight. Approximately 220 milliliters of lecithin-isopropyl myristate in a form of a liquid of a syrup consistency was formed.

Example 3

[0077] A beaker was prepared by measuring to a volume of 100 milliliters. It was considered important to measure the volume accurately rather than using beaker markings. An amount of Pluronic F127 NF (20 grams for a 20 percent gel, 30 grams for a 30 percent gel, 40 grams for a 40 percent gel) was mixed with 0.3 grams potassium sorbate NF. Refrigerated purified water was added in an amount sufficient to bring the volume to 100 milliliters. When all of the granules had been wet the gel was refrigerated. Solution took place upon cooling, taking 12 to 24 hours. The resulting 100 milliliters of Pluronic gel was kept refrigerated, since the gel will solidify at room temperature.

Example 4

[0078] Nine grams of carbamazepine in tablet form was ground in mortar and pestle. 4.3 milliliters of ethoxy diglycol was added and mixed to form a creamy paste. 13.2 milliliters of soya lecithin was added and mixed until smooth. The resulting 24 cc of solution was put into a 60 cc syringe. About 36 cc Pluronic F127 gel 20 percent (made according to Example 3) was placed in another syringe. The material was mixed well between syringes to yield 60 cc of carbamazepine organogel having a strength of 150 milligrams (mg) per milliliter. In some cases, the mixture was run through an ointment mill to reduce particle size.

Example 5

[0079] Sixty 100 milligram tablets of bupropion were ground and strained to form a fine powder. The bupropion

powder was dissolved in 30 cc purified water, placed in a filter and washed with 10 to 20 cc purified water. The filtrate was used to make a 20 percent Pluronic gel using the procedures from Example 3, substituting filtrate for an equivalent volume of water, and stored in a refrigerator. Thirteen milliliters of soya lecithin was mixed with one-half the bupropion Pluronic gel and mixed between syringes to form a first batch. Thirteen milliliters of soya lecithin was mixed with the second half of the bupropion Pluronic gel and mixed between syringes to form a second batch. To each batch was added sufficient Pluronic gel F127 (made according to example 3) to yield a total of two 60 cc batches of bupropion HC1 organogel having a strength of 15 milligrams per milliliter.

Example 6

[0080] 600 milligrams of fluoxetine HC1 (in the form of thirty 20 milligram capsules) was placed in a beaker and dissolved in approximately 18 cc of 95 percent ethyl alcohol. The solution was filtered through a filter funnel using fine filter paper. The residue was washed with 95 percent alcohol. The filtrate was heated, maintaining a temperature less than 850° C., to evaporate the alcohol to concentrate to 1 to 2 milliliters. 600 milligrams of isopropyl palmitate was combined with 600 milligrams of soya lecithin (granular), set aside and allowed to liquefy. Upon liquefaction, a thick syrupy consistency was obtained. 1.2 grams of the mixture was drawn into a 10 milliliter syringe and the alcoholic solution of fluoxetine HC1 was drawn into another syringe. The two syringes were attached together with a Luer-Luer adapter and the gel was thoroughly mixed. All of the organogel was then transferred into one syringe and the empty syringe was disconnected. Sufficient quantity of 20 percent Pluronic F127 gel (formed as described in Example 3) was drawn into the empty syringe to make a total of 6 milliliters when added to the volume in the other syringe. A Luer-Luer adapter was attached and the contents of the two syringes was remixed until a smooth creamy mixture was obtained. All the mixture was transferred into one syringe, the empty syringe was removed and the Luer-Luer adapter was removed.

[0081] A Luer-oral adapter was attached to the mixture and transferred to six 1 milliliter oral syringes, was filled with 1 milliliter of the gel. In this way, each syringe contained five 20 milligram doses, or ten 10 milligram doses to yield a total of 60 doses of fluoxetine in lecithin organogel having a strength of 10 milligrams per 0.1 milliliters.

Example 7

[0082] Twelve 250 milligram tablets of nefazadone were crushed in a mortar and pestle and put through a strainer. 4.8 milliliters of ethoxy diglycol (8 percent) was added and mixed. In cases in which all particles were not dissolved, 2 milliliters of Pluronic were added and mixed. 13.6 milliliters of soya lecithin were added and mixed. The resulting mixture was put into syringes with a Luer adapter and mixed well. Sufficient Pluronic F127 gel, prepared according to Example 3, was added to achieve a volume of 60 cc and mixed well to yield 60 cc of nefazadone organogel having a strength of 50 milligrams per milliliter.

Example 8

[0083] Thirty 40 milligram tablets of paroxetine were crushed and run through a strainer, discarding green coating

material. 4.8 milliliters of ethoxy diglycol was added to the powder and mixed in a mortar and pestle. Forty milliliters of Pluronic F127 gel 20 percent, formed according to Example 3, was added in graduated amounts to the powder and mixed until smooth using a spatula. 13.2 milliliters of soya lecithin was added and mixed well and the resulting material placed into syringes and sufficient quantity of Pluronic gel was added to bring the volume to 60 milliliters. In those such cases where particle size of the resulting material was too large, the cream was run through an ointment mill to yield 60 milliliters of paroxetine organogel having a strength of 20 milligrams per milliliter.

Example 9

[0084] Thirty 100 milligram tablets of sertraline were crushed into a fine powder and strained, discarding the yellow coating. Sufficient amount of Pluronic F127 gel 20 percent (formed according to Example 3) was added to achieve a volume of 38 milliliters and mixed well in a mortar and pestle until a smooth cream was achieved. This material was placed into syringes and mixed between the syringes to obtain a compact cream. 13.2 milliliters of soya lecithin was added and mixed well between the syringes using about 20 pumps. Sufficient quantity of Pluronic F127 gel 20 percent was added to yield 60 milliliters of sertraline gel having a strength of 15 milligrams per milliliter.

Example 10

[0085] Venlafaxine hydrochloride has a solubility in water of 572 mg/mL (adjusted to ionic strength of 0.2 M with sodium chloride). Forty-five 100 milligram tablets of venlafaxine were crushed and put through a strainer. The powder was dissolved in 15 cc purified water, the solution placed into a filter and washed with 10 cc purified water. The filtrate was used to make a 20 percent Pluronic gel using the procedures of Example 3 (substituting the filtrate for an equivalent amount of water) and placed into a refrigerator overnight. 13.2 milliliters of soya lecithin were drawn into a syringe with a Luer loc. The venlafaxine Pluronic gel was drawn into another syringe coupled to the first syringe and mixed well. Sufficient Pluronic F127 gel was added to achieve a volume of 60 cc with a strength of 75 mg. per cc.

Example 11

[0086] 15 grams of sodium valproate (Depakote) was ground in mortar and pestle. 4 mL of ethoxy diglycol was added and mixed well to form a creamy paste. 19.8 mL of soya lecithin was added and mixed until smooth. The resulting 24 cc of solution was put into 2 syringes with a Luer Loc and mixed well. The mixture was divided so that half is in each syringe. Using another 60 cc syringe, Pluronic 30% gel was added to each to bring each syringe to a volume of 45 mL.

Example 12

[0087] Paroxetine hydrochloride has a solubility in water of 5.4 mg/mL. Paroxetine (Paxil) gel was prepared, according to the procedures of example 8. A dosage of 40 mg per day was self-administered by a 59 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 210 days, blood was drawn and blood serum level of Paxil was determined to be 0 nanograms (ng) per mL, while typical reference levels are 49±26

ng/mL, indicating possible poor absorption or lab error. Clinical evaluation of the patient over a 210 day period of such transdermal administration indicated benefit to patient without GI side effects similar to that noted with oral preparation.

Example 13

[0088] Sertraline hydrochloride is slightly soluble in water and isopropyl alcohol and sparingly soluble in ethanol. Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 100 mg per day was self-administered by a 54 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 19 days, blood was drawn and blood serum level of Zoloft was determined to be 5 ng/mL, while typical reference levels are 30-200 mg/mL indicating possible limited absorption or lab error.

Example 14

[0089] Fluoxetine hydrochloride has a solubility in water of 14 mg/mL. Fluoxetine (Prozac) gel was prepared, according to the procedures of example 6. A dosage of 20 mg per day was self-administered by a 54 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7 days, blood was drawn and blood serum level of fluoxetine was determined to be 45 ng/mL, while the plasma level of the primary active metabolite norfluoxetine was also 45 ng/mL. There was evidence of patient benefit from the clinical evaluation.

Example 15

[0090] Carbamazepine is practically insoluble in water and soluble in alcohol and in acetone. Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 400 mg per day was self-administered by a 55 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 120 days, blood was drawn and blood serum level of Tegretol was determined to be 4.6 micrograms (μg) per mL, while typical therapeutic levels are 4-10 11 μg/mL indicating good absorption. There were no GI side effects and the patient demonstrated clinical improvement.

Example 16

[0091] Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 200 mg per day was self-administered by a 53 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 60 days, blood was drawn and blood serum level of Tegretol was determined to be 10.8 μg/mL, while typical therapeutic levels are 4-10 11 μg/mL indicating excellent absorption. There were no GI side effects and the patient demonstrated clinical improvement.

Example 17

[0092] Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 50 mg per day was self-administered by a 53 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 63 days, blood was drawn and blood serum level of Zoloft was determined to be 23 ng/mL,

while typical reference levels are 30-200 mg/mL. The patient demonstrated a good clinical response without GI side effects.

Example 18

[0093] Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 200 mg per day was self-administered by a 47 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 91 days, blood was drawn and blood serum level of Tegretol was determined to be less than 0.5 μ g/mL, while typical therapeutic levels are 4-10 μ g/mL, indicating poor absorption, lab error, or patient non-compliance.

Example 19

[0094] Bupropion is highly soluble in water. Bupropion (Wellbutrin) gel was prepared, according to the procedures of example 5. A dosage of 100 mg per day was self-administered by a 47 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 44 days, blood was drawn and blood serum level of Wellbutrin was determined to be less than 0.5 ng/mL, while typical therapeutic levels are 10-30 indicating poor absorption, lab error, or patient non-compliance.

Example 20

[0095] Fluoxetine gel was prepared, according to the procedures of example 6. Typically, a total daily adult dosage of fluoxetine as applied to the skin according to the present invention is between about 20mg and 200 mg, more preferably between about 120 mg and about 200 mg. Dosages for non-adults and/or non-human mammals may need to be adjusted, e.g. proportionally to body weight. A dosage of 20-60 mg per day was self-administered by 5 patients, including that of example 13 and also including a 44 year old male patient, a 53 year old female patient, a 47 year old male patient and a 36 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 30-180 day period of such transdermal administration indicated a clinical response ranging from complete remission of symptoms to moderate improvement.

Example 21

[0096] Fluoxetine gel was prepared, according to the procedures of example 6. A dosage of 80-160 mg per day was self administered by a 50 year old female by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7 days at the 80 mg dosage level blood was drawn and the blood serum of fluoxetine was determined to be 34 ng/mL fluoxetine and 25 ng/mL norfluoxetine, while typical reference levels are 50-480 ng/mL, indicating good absorption. There was evidence of patient benefit from the clinical evaluation. The dosage was then increased to 160 mg per day and administered by the same method. After 7 days at the 160 mg dosage level blood was drawn and the blood serum level of fluoxetine was determined to be 90 ng/mL fluoxetine and 25 ng/mL norfluoxetine, indicating good absorption. There was evidence of increased patient benefit at this higher dosage level which correlated posi-

tively with the higher plasma level. The patient has been receiving the medication continuously for a period of 5 months.

Example 22

[0097] Fluoxetine gel was prepared, according to the procedures of example 6. A dosage of 80-160 mg/day was self administered by a 38 year old female by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7 days at the 80 mg dosage level, blood was drawn and the blood serum level of fluoxetine was determined to be 25 ng/mL of fluoxetine and 25 ng/mL norfluoxetine. There was evidence of patient benefit from the clinical evaluation. The dosage was then increased to 160 mg per day and administered by the same method.

Example 23

[0098] Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 50-200 mg per day was self-administered by 6 patients, including those of examples 12 and 16 and also including a 60 year old male patient, a 53 year old male patient, a 48 year old male patient, a 38 year old male patient and a 47 year old male patient, by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 7-90 day period of such transdermal administration indicated responses ranging from complete resolution of depression to no noticeable response.

Example 24

[0099] Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 200-400 mg per day was self-administered by 6 patients, including those of examples 14, 15 and 17, and also including a 48 year old female patient, a 48 year old male patient and a 54 year old female patient, by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. The clinical evaluation of the patients over a 30-300 day period of such transdermal administration indicated responses ranging from moderate improvement to no positive clinical response.

Example 25

[0100] Paroxetine (Paxil) gel was prepared, according to the procedures of example 8. A dosage of 20 mg per day was self-administered by the patient of example 12 as well as by a 15 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. Clinical evaluation of the patients over a 30-210 day period of such transdermal administration indicated equivocal clinical improvement of the depression which may (or may not) have been related to the transdermally administered Paxil.

Example 26

[0101] Five 150 mg tablets of amitriptyline were crushed and run through a strainer. The powder was put into syringes with a Luer Loc and mixed well with 2 mL ethoxy diglycol. About 6 mL Pluronic Gel 20% was added and mixed well. 6.6 mL Soya Lecithin was added and mixed well. This

mixture was thinned to 30-mL total volume with Pluronic Gel 20% and mixed well. The resulting mixture having a strength of 25 mg/mL was placed in appropriate dispensing device.

Example 27

[0102] Amitriptyline (Elavil) gel was prepared, according to the procedure of example 26. A dosage of 25 mg per day was self-administered by a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 100 day period of such transdermal administration indicated an apparently good clinical response, comparable to that achieved with oral medication.

Example 28

[0103] Trazodone (Desyrel) gel was prepared, according to a procedure similar to that of example 7. A dosage of 50-150 mg per day was self-administered by 2 patients, including a 36 year old female patient and a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 42-90 day period of such transdermal administration indicated a good to excellent clinical response.

Example 29

[0104] Venlafaxine (Effexor) gel was prepared, according to a procedure similar to that of example 9. A dosage of 150-225 mg per day was self-administered by 2 patients, including a 54 year old female patient and a 55 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 15-165 day period of such transdermal administration indicated a response ranging from no clinical improvement to mild clinical improvement.

Example 30

[0105] Propranolol (Inderal) gel was prepared, according to a procedure similar to that of example 8 to produce a gel having a strength of 40 mg of propranolol per mL of gel. A dosage of 80 mg per day was self-administered by 2 patients, including a 36 year old female patient and a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 100 day period of such transdermal administration indicated results comparable to those achieved with oral medication.

Example 31

[0106] Bupropion (Wellbutrin) gel was prepared, according to a procedure described in example 5. A dosage of 150-200 mg per day was self-administered by 3 patients, including that of example 18, and also including a 38 year old male patient and a 53 year old female patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 5-45 day period of such transdermal administration indicated equivocal results.

Example 32

[0107] Valproic acid (Depakote) gel was prepared, according to a procedure similar to that of example 4. A dosage of 1000 mg per day was self-administered by a 38 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 30 day period of such transdermal administration indicated results comparable to those achieved with oral medication.

Example 33

[0108] Valproic acid (Depakote) gel was prepared according to the procedure of example 11. A dosage of 500-1000 mg was self administered by two male patients, ages 41 and 49. Administration was by application to the skin, for a period of at least one hour. Significant skin irritation occurred with one patient, but no gastrointestinal side effects were reported. Clinical evaluation of the patients over a period of two months revealed improvement, but upon longer term follow-up it appeared that other factors may have been responsible. After 28 days, blood was drawn and a serum valproic acid level of 26 $\mu\text{g/mL}$ was obtained for the 49 year old patient (while taking 250 mg twice daily), with a therapeutic reference range of 50-150 $\mu\text{g/mL}$. This indicated poor to fair absorption, and the dosage was raised to 500 mg twice daily, with a further improvement in clinical response. The 41 year old patient reported a good clinical response to an initial dosage of 250 mg administered twice daily, but a serum valproic acid level of only 1 $\mu\text{g/mL}$ was obtained. The dosage was increased to 500 mg twice daily, and a similar serum valproic acid level was obtained. The disparity between the clinical response and the plasma level might be explained either by laboratory error or placebo effect.

Example 34

[0109] A gel containing reboxetine (sold under the trade name Edronax) is prepared according to a procedure similar to that described in example 5 but using reboxetine in place of bopropion. The resulting mixture will be self administered by patients by application to the skin for a period of at least 1 hour. No skin irritation or gastrointestinal side effects are expected. Clinical evaluation of patients over a 5-45 day period of such transdermal administration is expected to indicate a good response to treatment.

Example 35

[0110] Nefazodone (Serzone) gel was prepared, according to a procedure described in example 7. A dosage of 100 mg per day was self-administered by a 61 year old (male, female) patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 21 day period of such transdermal administration indicated a good response to treatment.

Example 36

[0111] 1 gram of permoline tablets are crushed in a mortar and then dissolved in propylene glycol, just sufficient to effect dissolution. 3 mL of propylene glycol or 95% ethyl alcohol is added to form a paste. 6.6 mL soya lecithin is

added to the mixture in the mortar. The mixture is placed in two syringes with a Luer Loc and mixed thoroughly. Each syringe is filled to 30 mL Pluronic F127 20% gel and mixed between syringes to produce a mixture having a strength of 33 mg/mL. The mixture is put in an appropriate dispensing device.

Example 37

[0112] A 16-year-old female with an established diagnosis of Attention Deficit Disorder had been treated successfully with oral pemoline (Cylert) for about 6 months. To potentially decrease the risk of liver damage associated with long-term use, pemoline prepared according to the procedure of example 36 will be administered transdermally, by application to the skin in the post auricular region for a period of at least one hour, at two sites, twice daily. No skin irritation is expected. The clinical results are expected to be comparable to those obtained with the oral medication, although the dosage may have to be adjusted upwards to achieve adequate plasma levels, and more time may be required to achieve satisfactory plasma levels.

[0113] For psychiatric patients, some have received two or more psychopharmaceuticals, and in some cases, two or more of the above examples describe different evaluations for the same period of administration of a psychopharmaceutical agent.

[0114] Of the patients who have received prescriptions for one or more of the medications as described in the examples above, each had previously demonstrated a significant intolerance to oral administration of one or more medications, prior to instituting transdermal administration. The laboratory measures of plasma blood levels described above for transdermally administered fluoxetine and carbamazepine are believed to demonstrate good absorption transdermally using lecithin organogel matrix as the vehicle. Valproic acid and sertraline do not appear to be absorbed well or reliably. Valproic acid appears to cause skin irritation in some patients necessitating discontinuation. Both the laboratory measure of Bupropion and the patient clinical responses indicated poor or equivocal absorptions and results. Patient tolerance of transdermal administration has been good to excellent. Patients in the example above who suffered very severe GI side effects using oral preparations were more tolerant of the inconvenience of rubbing on the gel than were patients who had experienced only mild to moderate side effects. In general, more highly motivated and treatment-compliant patients also had a higher rate of sustained compliance.

[0115] Patients in the examples above were evaluated by means of a structured evaluation form depicted in FIG. 1, which was completed at a frequency of at least one time per week for each patient receiving transdermal medication according to the present invention. The patients were evaluated both for all present psychiatric symptoms as well as any side effects from currently-administered medications. In general, it is believed that patients with the most clear cut and uncomplicated diagnosis of major depression experienced the best results. In general, patients with severe personality disorders or with concealed substance abuse disorders did less well.

Example 38

[0116] 1800 mg of gabapentin in powder form is dissolved with 1 mL propylene glycol in syringes with a Luer Loc. 6.6

mL of Soya lecithin is added and mixed thoroughly between syringes. The resulting material is placed in a device for dispensing measured amounts.

Example 39

[0117] Gabapentin mixtures of 2% and 4% will be prepared by substituting 1200 mg gabapentin or 600 mg gabapentin in place of 1800 mg gabapentin, in example 38.

Example 40

[0118] Gabapentin, prepared according to Example 38 or 39, will be combined with either 3% or 5% Lidocaine in varying ratios.

Example 41

[0119] 4% gabapentin, prepared according to Example 38 or 39, will be combined with 7% carbamazepine and 7% amitriptyline.

Example 42

[0120] 2% gabapentin, prepared according to Example 38 or 39, will be combined with 2% carbamazepine and 1% Piroxicam, which is expected to yield better penetration into muscle tissue.

Example 43

[0121] Gabapentin, prepared according to Example 38 or 39, in concentrations ranging from 2%-6% will be combined with clonidine in concentrations between 0.2% and 0.3%.

Example 44

[0122] A 56-year-old woman had painful upper and lower extremity spasms as a result of spastic quadriplegia resulting from an injury. Oral gabapentin, an anticonvulsant, had been administered previously, but had caused a "drugged" feeling, one of the commonly reported side effects with this agent. It was believed that use of transdermal gabapentin might provide local relief by achieving high local tissue concentrations near the site of administration without correspondingly elevated blood plasma levels. It is known that other anticonvulsants, such as carbamazepine, are useful in reducing neurogenic pain. Gabapentin's solubility in water exceeds 10%, making systemic absorption less likely. Gabapentin prepared according to the procedure of example 38 was self-administered by application to the skin in the area of pain. The patient reported moderate relief of spasms over a period of one week, with no systemic side effects and no report of skin irritation.

Example 45

[0123] Six grams of amitriptyline powder was placed in 40 milliliters of Pluronic F127 33% gel and placed under refrigeration to dissolve. Two milliliters of ethoxy diglycol was added to 4.8 grams of carbamazepine and mixed to form a smooth paste. 16.4 grams of soya lecithin was added to the resulting paste and mixed well. The dissolved amitriptyline composition was added to the carbamazepine composition and sufficient Pluronic F127 20% was added to make 120 milliliters and the resulting composition was mixed well to yield a composition having 5% amitriptyline and 4% carbamazepine.

Example 46

[0124] 6 grams of doxepin was added to 20 milliliters Pluronic 33% F127 and put into a refrigerator to dissolve. 24 grams of ketoprofen and 12 grams of guaifenesin was added to 10 milliliters of 95% alcohol and mixed well. 26.4 milliliters of soya lecithin was added and mixed well and the doxepin composition was mixed with the ketoprofen/guaifenesin composition. The resulting mixture was added to sufficient Pluronic 33% to yield 120 milliliters. The resulting composition was mixed well to yield a composition having about 20% ketoprofen, 5% doxepin and 10% guaifenesin.

Example 47

[0125] 6 grams of doxepin was added to 26 milliliters Pluronic 33% and refrigerated to dissolve. 2 milliliters ethoxy diglycol was added 4.8 grams carbamazepine and mixed. The resultant mixture was added to 24 grams ketoprofen and six milliliters alcohol and the result was mixed well. 26.4 milliliters soya lecithin was added to the ketoprofen composition and mixed well. The doxepin composition was mixed with the carbamazepine/ ketoprofen composition and sufficient Pluronic 33% was added to yield 120 milliliters. The resultant composition was mixed well to yield a composition having about 20% ketoprofen, 4% carbamazepine and 5% doxepin.

Example 48

[0126] 0.15 grams sildenafil was crushed and strained and dissolved in 5 milliliters Pluronic 20% F127 and mixed

between syringes. 2.2 milliliters of soya lecithin was added and mixed. Sufficient Pluronic 20% was added to yield 10 milliliters and the resultant composition was mixed well to yield a composition having the strength of about 15 milligrams per milliliter.

Example 49

[0127] A mixture of Sildenafil 15 mg/ml was applied to the penis and scrotum of a 51 year old male. An immediate and strong erection resulted with sexual stimulation, without any irritation or burning. It is believed the composition will possess the therapeutic results claimed for orally administered Sildenafil, without any time delay, without any systemic GI side effects, and possibly without the degree of drug interaction with nitrates used in cardiac disease. It is believed that this will contribute both to the convenience of use of the pharmaceutical and to its safety.

Example 50

[0128] Compositions according the examples 45 through 47, 53, 55 were transdermally applied to numerous patients, for the purpose of treating pain including as described in other examples herein, with the results summarized in Table I below. The meaning of certain entries in Table I is indicated in Table II below. Blank results indicate no treatment at the pertinent site for this patient. Where a given line of Table I shows more than one site, one "best" (greatest pain relief) result if shown in bold.

TABLE I

Patient	Age	Gender	Surgery	Pain	Medication Wt % in lecithin organogel						
					Ketoprofen	Gabapentinm	Piroxicam	doxepin	carbamazepine	amitriptyline	guifenesin
A	50	2	2	3	10	3	4				
B	61	1	1	3				5			
B	61	1	1	3					4		
B	61	1	1	3	10	4	3				
C	41	2	1	2					4	5	
D	53	1	2	1	10	4	1				
E	57	2	2	3	10	4		5			1
F	57	2	2	3	10	4	3				
F	38	2	2	3				10	5		5
F	38	2	2	3		4			4		
F	38	2	2	3	10	4	1		4		
G	39	1	1	2	20	4		5	4		
H	61	1	1	3	10	4	3				
I	49	1	1	3	10	4	3				
I	49	1	1	3				5	5		10
I	49	1	1	3			4		4		
J	54	1	1	3					5	5	
K	40	1	2	3				5			
K	40	1	2	3	10		3	6			
L	55	2	2	2	10	4	3				
L	55	2	2	2				5			
M	38	1	2	1				4	5		
N	47	2	1	2	20	2				5	
N	47	2	1	2	10	4	1				
O	57	2	1	2	20	4		5			
O	57	2	2	2	10	4	3				
P	51	2	2	2	15	5		5			
Q	51	2	1	2	20			5			10
R	35	1	1	2					4	5	
R	35	1	1	2	10	4	1				
S	55	1	1	2	10	4	1				

TABLE I-continued

T	50	2	2	1	10	4	1					
U	45	1	2	2	10	4	3					
V	57	2	1	3					6			
V	57	2	1	3	10	4	1					
W	35	1	2	1	10	4	1					
X	46	1	1	3	10			5	4			
Y	48	1	1	3				5				
Y	48	2	1	3	10	4	1					
AA	53	2	2	1	10	4	1					
BB	58	2	1	3	20	4			4	Hand	1	
CC	59	1	1	2				5				
CC	59	1	1	2	10	4	1					
CC	59	1	1	2	10	4	5					
DD	58	1	1	2	10	4	3					
EE	45	2	2	2	10	4	3					
FF	44	2	1	3	10	4	3					
GG	35	1	1	3	20	4						
GG	35	1	1	3	20	4						
GG	35	1	1	3				5				
GG	35	1	1	3	20				5	5		
GG	35	1	1	3	20			5	5			
GG	35	1	1	3		5		5				10
HH	40	1	2	2	10	4	3					
II	40	1	2	3				5				
II	40	1	1	3	10	4	3	5				
JJ	45	1	2	2	10	4	3					
KK	37	2	2	2	10	4	1					
LL	54	1	1	3	10	4	3					
LL	54	1	1	3					4	5		
MM	42	2	1	3					4			
MM	42	2	1	3	10		3		4			
MM	42	2	1	3				5				
NN	41	1	2	2	10	4	3					

Result
(Best result in Bold)

Patient	Duration	shoulder	back	neck	elbow	Knee	Wrist	Arm	Ankle	Hip	Leg
A	2		0								
B	4				2.0						
B	12	2.0	2.0	2.0	2.0						
B	6							3.0			
C	2		1.0								
D	1			.0							
E	1		2.0			1.5					1.0
E	2	1.0	2.0				1.0				
F	2	2.0			3.0						
F	8	2.0						1.5			
F	4	2.0						1.0			
G	6					3.0					
H	4		2.0								
I	12						2.0				
I	1						1.0				
I	2						3.0				
J	2		1.5								
K	6	4.0									
K	4	1.0									
L	8	1.0						.0			
L	6		3.0					.0		1.5	2.0
M	2	1.5					.0				
N	3	3.0	3.0	4.0		1.0					
N	2.0	.0		2.0			2.0				
O	24	2.0		3.0							
O	24	1.0	.0								
P	2		4.0								
Q	1		2.0								
R	0					1.5					
R	1					.0					
S	16		1.0								
T	16					2.0	1.0		2.0		
U	2		.0								
V	8					3.0					
V	3					1.0					
W	8		1.0								
X	8		2.0	2.0	2.0						

TABLE I-continued

Y	4	2.0	2.0							
Y	4			1.5		1.5			.0	
AA	4		1.0							
BB	8		2.0						2.0	
CC	2			2.0		2.0		2.0		
CC	20		1.0	2.0		3.0	2.0			
CC	1					3.0		3.0		
DD	12			1.0			2.0			
EE	24	1.5		1.0						
FF	20	2.0								
GG	4			1.0			1.0			
GG	8			1.0			1.0			
GG	2						.0			
GG	2						2.0			
GG	2			1.0			2.5			
HH	4		1.0			1.0				
II	8		1.5							1.5
II	8		2.0							
JJ	2		1.0							
KK	8		1.0							
LL	6					1.0				
LL	2					.0				
MM	8		.0	4.0			2.0			1.0
MM	12		.0							
MM	4						2.0			1.0
NN	2		.0							

[0129]

TABLE II

Gender: 1 = male 2 = female

Surgery: 1 = one or more surgeries 2 = no
surgeries

Pain: 1 = mild 2 = moderate 3 = severe-sufficient to
produce observed tears

Duration: length of treatment trial in weeks

Result: 0 = no benefit
1 = mild benefit
2 = moderate benefit (greater than 25% pain reduction)
3 = major benefit (greater than 40-45% pain reduction)
4 = almost complete relief (greater than 80% pain reduction)

[0130] Certain results drawn from the information of Table I are summarized in Table III and IV.

TABLE III

Site	N (Number of data points)	Percent reported pain relief					Total
		None	Mild	Mild- moderate	moderate	Major	
Wrist	13	16.7	33.3	8.3	41.7		
Shoulder	14	7.1	21.4	14.3	42.9	7.1	7.1
Elbow	5		40	20	20	20	
Back	25	24	32	8	28	8	
Arm	7	28.6	14.3	14.3	28.6	14.3	
Neck	11	9.1	18.2		45.5	9.1	18.2
Knee	13	15.4	46.2	15.4	7.7	15.4	

[0131]

TABLE IV

	<u>(percent reported pain relief)</u>						
	N.	None	Mild	Mild-moderate	moderate	Major	Total
Best result without tricyclic	36	16.7	36.1	8.3	27.8	8.3	2.8
Best result with any tricyclic	20	10	10	20	35	15	10
Either tricyclic -sole agent	7		14.3	14.3	42.9	14.3	14.3
Best result	25	16	44	4	28	8	

TABLE IV-continued

(percent reported pain relief)							
	N	None	Mild	Mild-moderate	moderate	Major	Total
with ketoprofen gabapentin piroxicam							
Best result	43	18.6	32.6	14	23.3	7	4.7
without doxepin							
Best result	13		7.7	7.7	53.8	23.1	7.7
with doxepin							

Example 51

[0132] A 51 year old female administered a composition prepared according to example 46, containing 20% ketoprofen, 5% doxepin, and 10% guaifenesin to her back for a period of 2 weeks. She reported moderate pain relief, lasting several hours, after each application. She reported no skin irritation nor any other side effects. Oral medications had produced no relief, and had caused significant GI side effects.

Example 52

[0133] A 34 year old man administered a composition containing 20% ketoprofen, 4% carbamazepine, and 5% doxepin to a very severely scarred wrist that had undergone 4 surgeries for carpal tunnel syndrome. He reported moderate pain relief, lasting for several hours after each application. No other treatment, including opiate oral pain medication, had been effective in providing even minor pain relief.

Example 53

[0134] 24 grams ketoprofen and sufficient guaifenesin to result in a 10% final guaifenesin concentration, was mixed well with 10 milliliters 95% alcohol. 1200 mg gabapentin was dissolved in one ml propylene glycol in a syringe with a luer loc. 26.4 ml of soya lecithin was added to the ketoprofen-guaifenesin-alcohol mixture and mixed well. The resulting mixture was added to the gabapentin-propylene glycol mixture and mixed well. 4.8 gm of carbamazepine was combined with the resultant combination and mixed well to form a smooth paste. The resulting paste was combined with the ketoprofen-guaifenesin-alcohol-gabapentin mixture and mixed well with sufficient pluronic to yield 120 ml of a composition containing ketoprofen 20%, carbamazepine 4%, gabapentin 4%, guaifenesin 10%.

Example 54

[0135] A 58 year old female with damage to her cervical spinal cord with a resultant spastic quadraparesis reported moderate relief of both pain and muscle spasms when she applied a mixture prepared generally according to example 53, containing ketoprofen 20%, carbamazepine 4%, gabapentin 4%, guaifenesin 10% for a period of 8 weeks to her back and hip. She had been unable to tolerate both oral carbamazepine and oral gabapentin because of systemic side effects, including skin rash with the carbamazepine and dizziness and sedation with the gabapentin. She experienced no skin irritation nor other side effects with the transdermal formulation.

Example 55

[0136] Six grams of doxepin powder combined with 26 milliliters pluronic and placed in the refrigerator until dissolved. 1200 mg gabapentin was mixed with 1 ml propylene glycol and placed in a syringe with luer lock. 6.6 ml of soya lecithin was added and mixed well between syringes. 24 gm of ketoprofen and 8 milliliters alcohol was mixed well between two syringes with luer loc. The doxepin mixture was mixed well with the gabapentin mixture and subsequently the ketoprofen mixture was added and mixed well. Sufficient pluronic 20% (about 54 ml) was added to yield 60 ml of a composition having about 20% ketoprofen, 4% weight percent gabapentin and 5% weight percent doxepin.

Example 56

[0137] A 57 year old female applied a mixture, prepared generally according to example 55, containing ketoprofen 20%, gabapentin 4%, and doxepin 5% for a period of 8 weeks to her neck and reported major relief. She applied the same mixture to her shoulder and reported moderate relief. A mixture that substituted piroxicam for the doxepin produced only mild shoulder relief.

Example 57

[0138] A 35 year old man with a history of knee injury with vascular compromise and 3 surgeries applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% amitriptyline to his knee, and reported mild to moderate pain relief, without skin irritation nor other side effects.

Example 57A

[0139] A 41 year old woman with history of back surgery applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% gabapentin to her back for a period of 2 weeks. She reported mild pain relief.

Example 58

[0140] A 53 year old man with a history of two total bilateral knee replacements applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% amitriptyline to both knees for a period of 4 weeks. He reported no pain relief.

Example 58A

[0141] A 54 year old man with a history of 7 back surgeries applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% amitriptyline to his back for a period of 2 weeks. He reported mild to moderate pain relief, over and above that he was receiving from a transdermal opiate medication (Duragesic). He reported no side effects, and specifically no skin irritation.

Example 59

[0142] A 38 year old man with a history of shoulder strain applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% amitriptyline to his shoulder for a period of 2 weeks. He reported mild to moderate pain relief, and reported no skin irritation nor other side effects.

Example 61

[0143] Sufficient carbamazepine and gabapentin was added to a combination of soya lecithin and pluronic to yield a lecithin organogel having about 4% carbamazepine and 5% gabapentin.

Example 62

[0144] A 42 year old woman with a history of 3. back surgeries and cervical degenerative disc disease applied a mixture, prepared according to example 61, containing 4% carbamazepine and 5% gabapentin to her neck and reported total relief of pain. She reported no side effects, and no skin irritation. She noted the complete and rapid resolution of a migraine like headache at the same time. Administration of the same mixture to her arm and her wrist, affected by a diagnosed condition of reflex sympathetic dystrophy, yielded moderate pain relief.

Example 63

[0145] 3.6 grams gabapentin was dissolved with 5.4 ml ethoxy diglycol using a mortar and pestle. 9.6 grams ketoprofen and 2.7 grams piroxicam were added and the resultant composition mixed well. 19.8 milliliters soya lecithin was added and resultant mixture mixed well and added to a sufficient quantity of 20% pluronic gel to yield 90 milliliters of a composition having about 10 percent ketoprofen, 4% gabapentin and 3% piroxicam.

Example 64

[0146] 3.6 grams gabapentin was dissolved with 5.4 ml ethoxy diglycol using a mortar and pestle. 9 grams ketoprofen and 0.9 grams piroxicam were added and mixed well. 19.8 milliliters soya lecithin was added to the resultant mixture and mixed well. Sufficient amount of pluronic gel 20% was added to yield 90 milliliters of a composition having approximately 10% ketoprofen, 4% gabapentin and 1% piroxicam.

Example 65

[0147] 12 g doxepin was mixed with 50 ml Pluronic F127 33% and placed in a refrigerator to dissolve. 12 g gabapentin was dissolved in 9 ml ethoxy diglycol and mixed to form a smooth paste. 52.8 ml of soya lecithin was added and mixed well. The doxepin/Pluronic mixture was added and mixed well. Sufficient quantity of Pluronic F 127 20% was added to produce 240 ml of a composition having about 5 wt % gabapentin and 5 wt % doxepin.

Example 66

[0148] A 36 year old man with a knee injury involving joint surface damage and vascular compromise applied a mixture, prepared generally according to Example 65 to his knee several times per day. He reported moderate to major (40%) relief of pain that persisted for 4 to 6 hours. An earlier trial of carbamazepine-amitriptyline gel produced no relief when applied to his knee.

Example 67

[0149] 6 gm doxepin was mixed with 18 ml of Pluronic 33% to and placed in a refrigerator to dissolve. 6 gm gabapentin was ground in a mortar and pestle to a fine

powder, added to 6 ml ethoxy diglycol and mixed to form a smooth paste. 12 gm guaifenesin was added and mixed well. 26.4 ml soya lecithin was added and mixed well. The doxepin/Pluronic mixture was added and mixed well. Sufficient quantity of Pluronic gel (25.2 ml of 33% Pluronic, although 30% or 20% Pluronic can be used), was added to produce 120 ml of a composition having about 5 wt % gabapentin, about 5 wt % doxepin and about 10 wt % guaifenesin.

Example 68

[0150] A 55 year old woman with a back and shoulder injury sustained as a nursing care provider applied a mixture, prepared generally according to Example 67, to her back three times per day for a period of two weeks and achieved major relief. She applied the same mixture to her hip and leg and reported moderate to major relief. A mixture containing only doxepin provided only moderate relief to her back, and mild to moderate relief to her hip and leg. A mixture that contained only ketoprofen, gabapentin and piroxicam provided only mild relief to her back.

Example 69

[0151] A 59 year old woman with cervical and back strain applied a mixture, prepared generally according to example 51, but without steps involving ketoprofen) containing about 5 wt % doxepin and about 10 wt % guaifenesin, to her neck for a period of two weeks, two to four times per day, and achieved total relief. She applied the same mixture to her back and achieved major to total relief.

Example 70

[0152] 4.5 gm of doxepin HCl was dissolved using 2.5 ml 95% alcohol and mixed well between syringes. It is also possible to mix the doxepin with 5 ml Pluronic 20% and place in a refrigerator to dissolve. Sufficient quantity of 20% Pluronic F127 was added to produce 90 ml of a composition having about 5 wt % doxepin. Preferably this and other disclosed compositions are protected from light.

Example 71

[0153] A 61 year old man with injuries to his back, neck and arm applied a mixture (prepared generally according to Example 70) to his neck four times per day and achieved major relief. He applied the same mixture to his elbow and achieved moderate relief.

Example 72

[0154] A formulation of 7% antidepressant and about 10% muscle relaxant was prepared by dissolving 3.15 g of trimipramine and 4.5 g of guaifenesin in a mixer jar using 2.7 mL of ethoxy diglycol. About 9.9 mL of soya lecithin was added and the mixture was mixed well. Sufficient quantity of Pluronic F127 NF (20%) to make total volume of about 45 mL was added and mixed well.

Example 73

[0155] A gel formulation of 30% NTHE was prepared from 36 g of celecoxib, 7.2 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (20%) to make total volume of 120 mL.

Example 74

[0156] A gel formulation containing about 7% antidepressant and about 13% muscle relaxant was prepared from 14.4 g of doxepin, 31.2 g of guaifenesin, 12 mL of ethoxy diglycol, 52.8 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 240 mL.

Example 75

[0157] A gel formulation containing 5% antiepileptic was prepared from 6 g of lamotrigine, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 76

[0158] A gel formulation containing 10% adrenergic agonist was prepared from 12 g of crushed tizanidine, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 77

[0159] A gel formulation containing 10% muscle relaxant was prepared from 12 g of crushed metaxalone, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 78

[0160] A gel formulation containing 10% muscle relaxant was prepared from 12 g of crushed carisoprodol, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 79

[0161] A gel formulation containing 10% methocarbamol was prepared from 12 g of crushed methocarbamol, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 80

[0162] A gel formulation containing 10% muscle relaxant was prepared from 12 g of crushed dantrolene sodium, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 81

[0163] A gel formulation containing 7% antidepressant, 10% muscle relaxant was prepared from 8.4 g of crushed doxepin, 12 g of chlorzoxazone, 6 mL of ethoxy diglycol, 26.4 mL of soya lecithin and sufficient quantity of Pluronic F127 NF (33%) to make total volume of 120 mL.

Example 82

[0164] A series of experiments in human subjects were performed using various combinations of pharmaceuticals. The results are indicated in FIG. 2.

[0165] Values of pain relief as rated by the patients are provided for each body part for which the medication was administered. The scale used in FIG. 2, is as follows:

0 = None	no benefit or equivocal benefit
1 = Mild	less than 15% pain reduction
1.5 = Mild-moderate	15-25% pain reduction
2.0 = Moderate	25-33% pain reduction
2.5 = Moderate-major	33-45% pain reduction
3.0 = Major	45-60% pain reduction
3.5 = Major-total	60-80% pain reduction
4.0 = Total	greater than 80% pain reduction

[0166] For each body part and for each percentage composition of each compounded medication, the individual ratings as well as a mean, which is the statistical mean of the values given according to the scale listed above, are provided. For example, 3 patients were administered doxepin 5% to their back, and the mean level of relief was 2.333. By contrast, 13 patients received the 5%/10% doxepin-guaifenesin combination, and their mean level of pain relief was 2.885. Results for 7/10 and 10/10 compositions of doxepin guaifenesin are also given, and the mean for the entire sample of dox-guai in all combinations is provided at the end of the section, namely 2.722.

[0167] The abbreviations used in FIG. 2 are as follows:

Abbreviations	Generic Pharmaceutical names
c-dox-gu	carbamazepine doxepin guaifenesin
c-gab-do	carbamazepine gabapentin doxepin
carb	carbamazepine
carb-ami	carbamazepine amitriptyline
carb-gab	carbamazepine gabapentin
dox	doxepin
dox-chl	doxepin chlorzoxazone
dox-guai	doxepin guaifenesin
g-dox-gu	gabapentin doxepin guaifenesin
gab-dox	gabapentin doxepin
k-ca-dox	ketoprofen carbamazepine doxepin
k-car-pi	ketoprofen carbamazepine piroxicam
k-dox-ch	ketoprofen doxepin chlorzoxazone
k-dox-gu	ketoprofen doxepin guaifenesin
k-dox-pi	ketoprofen doxepin piroxicam
k-g-do-g	ketoprofen gabapentin doxepin guaifenesin
k-gab	ketoprofen gabapentin
k-gab-ami	ketoprofen gabapentin amitriptyline
k-gab-do	ketoprofen gabapentin doxepin
k-gab-gu	ketoprofen gabapentin guaifenesin
k-gab-pi	ketoprofen gabapentin piroxicam
k-pi	ketoprofen piroxicam
la-li-gu	lamotrigine lidocaine guaifenesin
lam-chl	lamotrigine chlorzoxazone
n-dox-ch	naproxen doxepin chlorzoxazone
naproxen	naproxen
tri-chl	trimipramine chlorzoxazone

[0168] Based on the results described herein, doxepin appears to be an effective pain relief medication when administered transdermally and appears to be substantially free of side effects when administered transdermally as described herein.

[0169] Doxepin appears to provide about three times the positive response rate compared to at least some other pharmaceutical agents described herein, regardless of

whether such other pharmaceutical agents are administered singly or in combination. Doxepin appears to be substantially more effective than amitriptyline as a pain, e.g., neuropathic pain agent when administered transdermally. This appears to be true regardless of whether doxepin is administered as a single agent or is administered in combination with other pharmaceuticals as described herein.

[0170] Carbamazepine appears to provide positive effects as a pain, e.g., neuropathic pain agent, at least in properly selected patients. Carbamazepine appears to cause a rash in at least some patients, requiring its discontinuation.

[0171] These side effects appear similar to those that are noted for oral administration of carbamazepine. Gabapentin appears to be free of side effects when administered transdermally. Although some patients appear to derive some benefit from a combination of transdermally administered ketoprofen, gabapentin, and piroxicam, the effect appears to be relatively weak compared to the effect provided by doxepin.

[0172] Guaifenesin appears to provide benefit as an adjunctive treatment, of painful spasticity. For the patient population described herein, amitriptyline appeared to offer limited pain relief when administered transdermally. It appears that combining gabapentin with doxepin may offer some additional benefit. The addition of guaifenesin to doxepin may be of particular value when painful spasticity is present.

[0173] In view of the above, the invention provides treatment to patients for whom oral delivery is suboptimal, such as patients who experience gastrointestinal or other side effects, patients who experience poor absorption for orally delivered pharmaceuticals and/or patients who benefit from delivery over an extended period or a relatively rapid delivery or higher rate of increase of plasma levels. The present invention achieves delivery of therapeutic amounts of pharmaceuticals, for at least some patient populations, substantially without skin irritation, gastrointestinal or other side effects associated with orally-delivered pharmaceuticals, especially psychopharmaceuticals, and yields clinical benefits comparable to or greater than those received by patients to whom corresponding pharmaceuticals were administered orally. In view of the above reasons, particularly effective pain medications are those described in examples 65, 67, 69 and 70.

[0174] A number of variations and modifications of the invention can also be used. It is believed that blood plasma levels may be increased by providing for two or more transdermal applications per day and/or applying a transdermal composition to two or more sites.

[0175] In at least one case, application of a Prozac gel formulation twice daily appeared to approximately double the plasma level. It is believed that an approach such as applying a Prozac gel formulation twice daily to two sites will yield middle range therapeutic levels of about 140-250 ng/ml. At least partially on the basis of the results described herein for fluoxetine, it is believed olanzapine (sold under the trade name Zyprexa) or a fluoxetine/olanzapine mixture in a lecithin organogel will prove useful.

[0176] Other types of psychotropic or psychopharmaceutical medications for which the described transdermal delivery may be used including psychostimulant medications.

One example of a psychostimulant medication is Methylphenidate (sold under the trade name Ritalin) used in the treatment of attention deficit hyperactivity disorder (ADHD). Methylphenidate typically has a 2-4 hour duration of action necessitating frequent dosing of a patient which is particularly difficult to accomplish with children in school. It is believed that by using transdermal administration, it will be possible to achieve an extension of effective dosing throughout the day, eliminating the need for frequent oral medication administration. It is believed that transdermal administration will also eliminate peaks and valleys of blood plasma levels which, it is believed, will be more clinically effective. It is believed similar results will be obtained with other pharmaceuticals, for example, Dextroamphetamine (under the trade name Dexedrine) although it is believed the need is less acute since a time release "spansule" form of the medication is available which typically has a 5-6 hour duration of action. Another group of psychotropic medications which, it is believed, will benefit from transdermal delivery includes antipsychotic medication such as those used in the treatment in schizophrenia.

[0177] Embodiments of the invention include, but are not necessarily limited to, use by patients with enteric absorption deficits.

Equivalents

[0178] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

What is claimed is:

1. A method for treating pain in a subject comprising contacting said subject with a transdermal composition comprising:

(a) an amine containing compound having biphasic solubility in an amount effective to treat pain in said subject; and

(b) a pharmaceutically acceptable carrier suitable for transdermal delivery of the amine containing compound to said subject.

2. The method of claim 1, wherein the amine containing compound is an antidepressant compound.

3. The method of claim 54, wherein the antidepressant compound is a tricyclic antidepressant compound.

4. The method of claim 1, wherein the amine containing compound is doxepin.

5. The method of claim 1, wherein the pharmaceutically acceptable carrier comprises a lecithin organogel.

6. The method of claim 1, wherein the pharmaceutically acceptable carrier comprises a Pluronic F127 gel.

7. A method for treating pain in a subject comprising contacting said subject with a transdermal composition comprising:

(a) doxepin; and

(c) a pharmaceutically acceptable carrier suitable for transdermal delivery of the doxepin to said subject.

8. The method of claim 59, wherein the pharmaceutically acceptable carrier comprises a lecithin organogel.

9. The method of claim 59, wherein the pharmaceutically acceptable carrier comprises a Pluronic F127 gel.

10. A method for treating pain in a subject comprising contacting said subject with a transdermal composition comprising:

(a) a muscle relaxant; and

(c) a pharmaceutically acceptable carrier suitable for transdermal delivery of the muscle relaxant to said subject.

11. The method of claim 62, wherein the muscle relaxant is selected from the group consisting of guaifenesin, chlorzoxazone, dantrolene sodium, metaxalone, carisoprodol, and combinations thereof.

12. The method of claim 62, wherein the muscle relaxant is guaifenesin.

13. The method of claim 62, wherein the pharmaceutically acceptable carrier comprises a lecithin organogel.

14. The method of claim 62, wherein the pharmaceutically acceptable carrier comprises a Pluronic F127 gel.

15. A method for treating pain in a subject comprising contacting said subject with a transdermal composition comprising:

(a) guaifenesin; and

(c) a pharmaceutically acceptable carrier suitable for transdermal delivery of the guaifenesin to said subject.

16. The method of claim 67, wherein the pharmaceutically acceptable carrier comprises a lecithin organogel.

17. The method of claim 67, wherein the pharmaceutically acceptable carrier comprises a Pluronic F127 gel.

18. A method for treating pain in a subject comprising selecting a subject in need of pain treatment and contacting said subject with a transdermal composition comprising:

(a) doxepin; and

(c) a pharmaceutically acceptable carrier suitable for transdermal delivery of the doxepin to said subject.

19. A method for treating pain in a subject comprising selecting a subject in need of pain treatment and contacting said subject with a transdermal composition comprising:

(a) guaifenesin; and

(c) a pharmaceutically acceptable carrier suitable for transdermal delivery of the guaifenesin to said subject.

* * * * *



Differential Effects of Antidepressants

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Examples:

Reboxetine^a and Viloxazine

NARIs have no direct action on noradrenergic receptors or other monoamine transmitters.

Main pharmacological effects include:

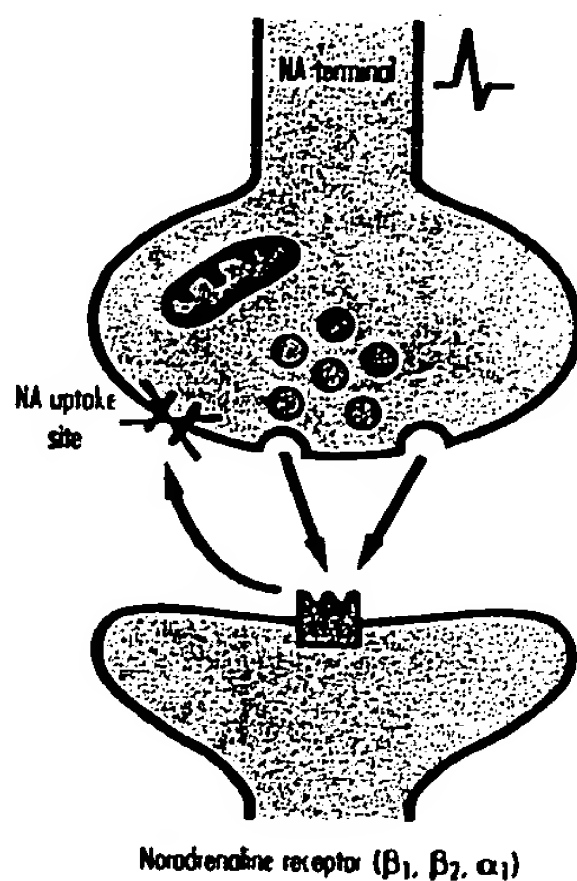
inhibition of noradrenaline reuptake;

increased intersynaptic noradrenaline;

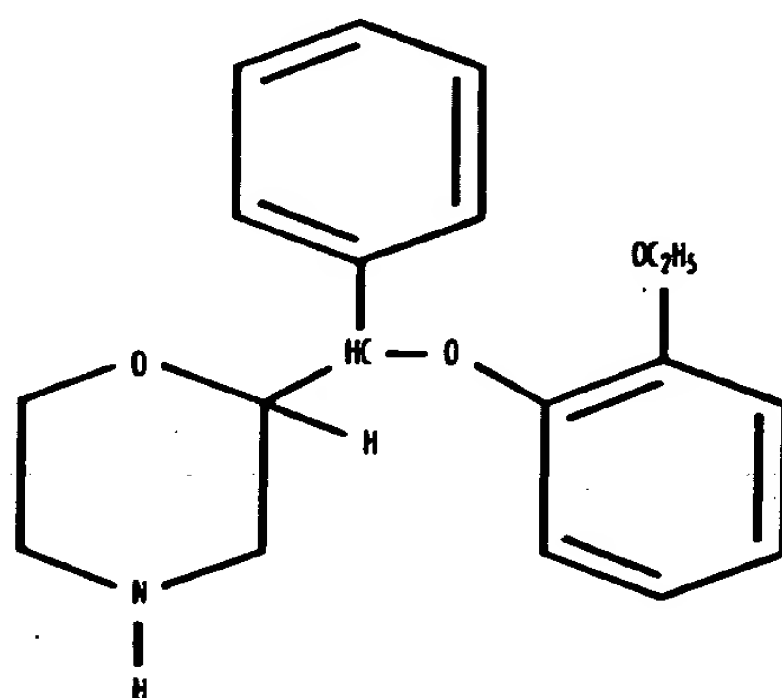
and adaptive decrease in postsynaptic β_2 -receptors and

inhibitory presynaptic α_2 -adrenoceptors.

^a Now termed a specific noradrenaline reuptake inhibitor (NARI).



Reboxetine^a



Viloxazine

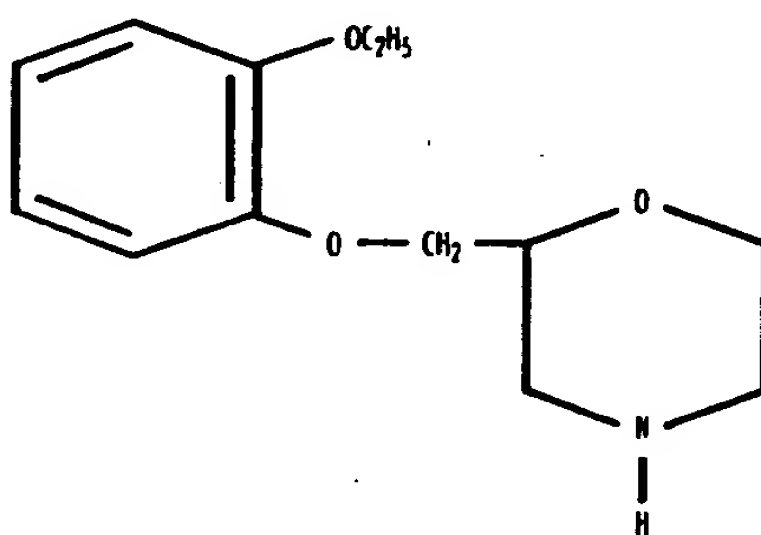


Figure 11

Action of NARIs on noradrenaline reuptake.

Although the serotonin–dopamine interaction is the most probable cause of the motor side-effects, recent research also

indicates that some SSRIs (such as fluoxetine and fluvoxamine) sensitize the α_2 -receptors in the rubrocerebellar region

way. In this region of the brain, dopamine appears to act as a hedonic transmitter: its release causes a pleasurable effect. This, incidentally, is one of the main reasons why drugs of dependence are abused (because they release dopamine in the mesocortical region) and why the monoamine oxidase inhibitors (MAOIs) and dopaminergic activities of drugs such as bupropion do not cause sexual dysfunction.

Besides reducing libido in both male and female patients, the SSRIs can also enhance the brain stem–dorsal horn spinal pathway which inhibits ejaculation. Clearly the action of the SSRIs on sexual activity is complex, but the primary role played by the serotonergic system is the result of the beneficial action of non-specific serotonin receptor antagonists such as cyproheptadine which can reverse the SSRI-induced sexual dysfunction. However, the sedative effect of cyproheptadine (resulting from its antihistaminic action) precludes its routine use in this condition.

The brain-stem vomiting centre can be triggered by drugs that stimulate the 5HT₃-receptors, which are situated on the chemoreceptor trigger zone. The slight nausea experienced by many patients early in treatment with an SSRI is attributed to stimulation of central and gastroin-

testinal 5HT₃-receptors. Drugs that block the 5HT₃-receptors, such as ondansetron and granisetron, antagonize the nauseant effects of the byproducts of cancer chemotherapy.

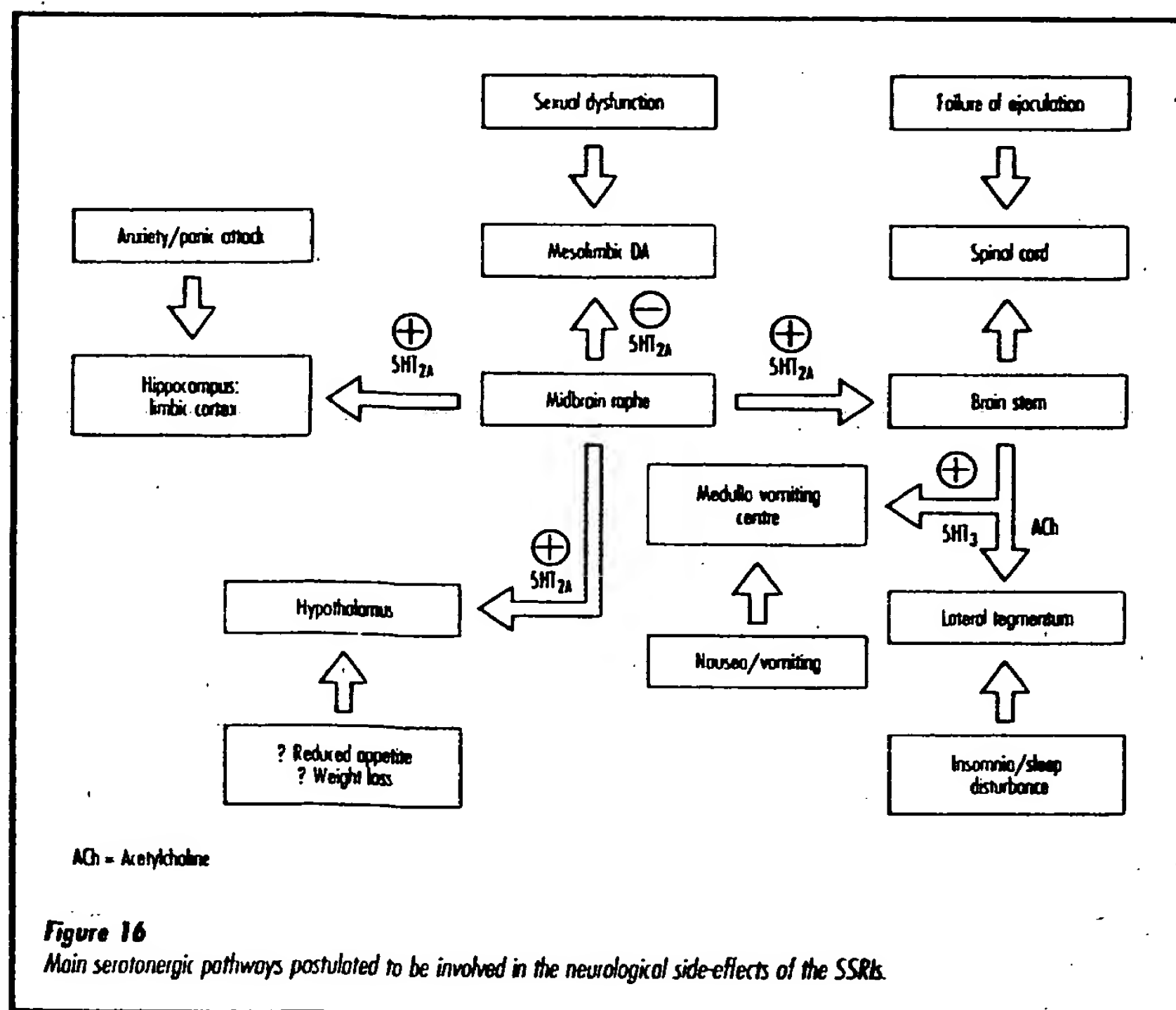
In addition to the direct effect of the SSRIs on the vomiting centre, there is also evidence that there is enhanced activity of the brain stem–hypothalamic pathway which mediates appetite and feeding behaviour. This could play a role in the anorexia and weight loss that occurs in some patients receiving an SSRI.

The main serotonergic pathways which appear to be used in the aetiology of the neurological side-effects of the SSRIs are summarized in *Figure 16*.

Extending the scope of therapeutic action of the SSRIs

There is preliminary evidence that the SSRIs are useful in the treatment of the following conditions:

- *Pre-menstrual syndrome.*
- *Premature ejaculation.*
- *Fibromyalgia.*
- *Chronic pain syndromes.*
- *Negative symptoms of schizophrenia.*



However, none of these studies has been subject to double-blind placebo-controlled trials, and so the use of the SSRIs in these conditions rests largely on anecdotal reports.

With regard to the use of antidepressants in chronic pain, the only extensive placebo-controlled studies have involved the TCAs. The results of these studies suggest that antidepressants that inhibit

the reuptake of both noradrenaline and serotonin are more effective than second-generation antidepressants such as mianserin, maprotiline, trazodone or zimelidine.

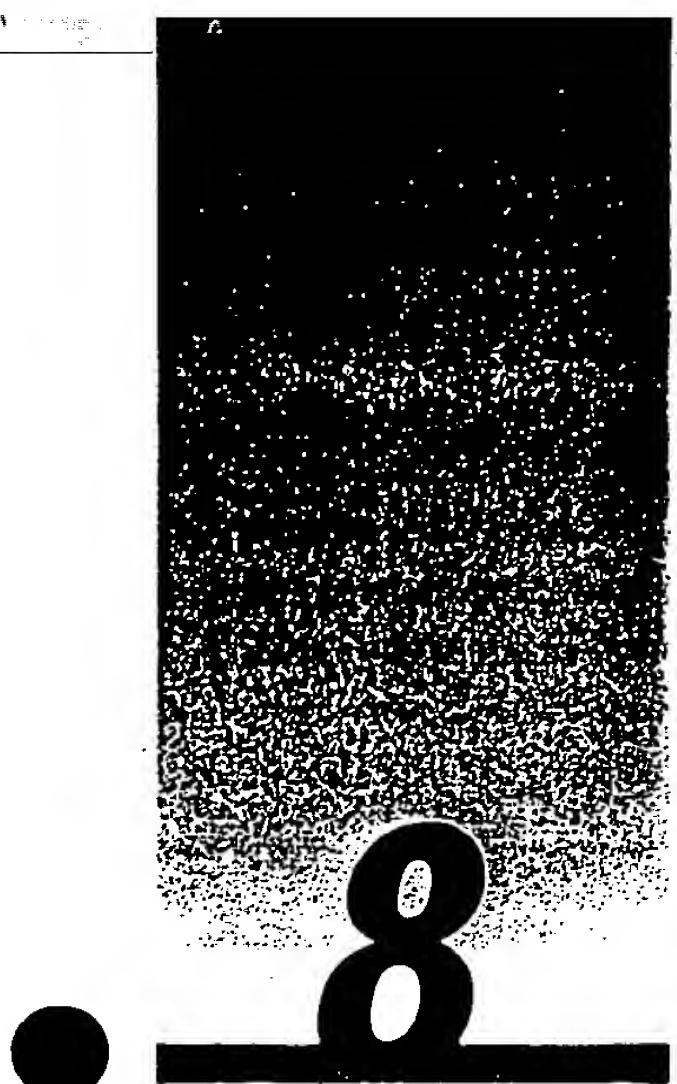
Although the precise mechanism by which the antidepressants bring about their analgesic effects is unknown, it would appear that they exert them independently of their antidepressant effects. One possibility is that antidepressants that bring

about chronic pain relief do so by activating opioid receptors directly or indirectly.

Summary

It would appear that the SSRIs are of little benefit in the treatment of pain associated with fibromyalgia or diabetic neuropathy, low back pain or rheumatic pain. There is no evidence that the SSRIs have any beneficial effects in treating either the positive or the negative systems of schizophrenia.

Role of noradrenaline in depression



The monoamine hypothesis postulates that the primary cause of depression results from a malfunction of the noradrenergic and serotonergic systems in the brain. Despite the extensive studies of postmortem brains and body fluids from depressed patients and suicide victims, such studies have yielded mixed and sometimes confusing results. Nevertheless, there is evidence for a dysregulation of noradrenergic neurons in the cortical and hypothalamic areas of the depressed patient. For example, after the acute infusion of the α_2 -adrenoceptor agonist clonidine into a depressed patient, the release of growth hormone from the pituitary gland is reduced. This response remains blunted even after recovery of the patient, which suggests that it could be a trait marker of the condition. Further evidence implicating an abnormality in noradrenergic function in depression arises from studies of the peripheral noradrenergic system. It has been shown that there is an increased release of noradrenaline in patients with major depression, which results in a decreased β -adrenoceptor responsiveness (as shown, for example, by a decreased responsiveness of the β -receptors on lymphocyte membranes to an

isoprenaline challenge) and an increased activity of the α_2 -adrenoceptors on the platelet membrane. This could be used as a model for the inhibitory presynaptic α_2 -receptors which reduce noradrenaline release from the neurons.

There is accumulating evidence that the noradrenergic system modulates drive and motivation, whereas the serotonergic system modulates impulsiveness and mood. However, some of these functions, such as sleep disturbance and anxiety, overlap which is understandable in view of the close interrelationship of these two neurotransmitter systems within the brain. Nevertheless, the noradrenergic system plays a key role in learning, memory, sleep, arousal and adaptation. It has been shown that, although the locus coeruleus, the main nucleus that controls noradrenergic activity in the brain, is relatively quiescent during eating, sleeping and other behaviours, its activity increases whenever novel external stimuli are presented. Thus it would appear that noradrenaline plays an important role in the disturbance of vegetative function associated with affective and cognitive disorders, and anxiety. In addition, the locus coeruleus plays an essential role in adaptive and arousal responses. From experimental studies, it has been shown

that it fires in a phasic manner when the animal is subjected to a threatening stimulus. It would appear that this system becomes desynchronized in depression or when there is chronic exposure to stress, leading to malfunctioning of the central and peripheral sympathetic nervous systems.

Summary

There is evidence of altered central and sympathetic activity in the depressed patient, which may result from a primary malfunction of the main noradrenergic cell body area, the locus coeruleus. Effective antidepressant treatment may compensate for this.

Pharmacological properties of drugs that act on the brain's noradrenergic system

There was major advance in the treatment of depression with the development of the second generation of antidepressants; these combined the efficacy of the conventional TCAs with improved compliance as a result of the reduction in the adverse side-effects. Of the different classes of second-generation antidepressants that have been developed in the last 20 years, the SSRIs have achieved particular promi-

nence. However, now they have been used extensively, it is becoming apparent that the SSRIs have adverse effects, particularly on the gastrointestinal tract and on sexual function, and many patients find this intolerable. Furthermore, there is growing evidence that the SSRIs are not as effective as the TCAs in the treatment of

severe depression. This has led to the development of antidepressants such as venlafaxine and milnacipran which selectively inhibit the reuptake of noradrenaline and serotonin (but which lack the cardiotoxic effects of the TCAs), and, more recently, a new generation of selective NARIs. As shown in *Table 13*, it is

Table 13

Effect of some antidepressants on neurotransmitter receptors in the brain tissue in vitro.

	K_i (nmol/l) of adrenoceptors					
	α_1	α_2	β_1	β_2	5HT _{1A}	5HT ₂
Representative SSRIs						
Fluoxetine	5990	>10 000	>5000	>10 000	>10 000	>1000
Sertraline	300	>5000	>5000	>5000	>10 000	>1000
SNRI						
Venlafaxine	>10 000	>10 000	>10 000	>10 000	>10 000	>7500
NARI						
Reboxetine	>10 000	>10 000	>10 000	>1000	>1000	>1000
Representative TCAs						
Amitriptyline	170	540	>5000	1200	1000	8
Clomipramine	38	3300	>5000	190	5200	63

K_i Values greater than 500 nmol/l imply that the drug would have no effect on the functional activity of the receptors in in vitro.

The inhibitory constant, K_i, is a measure of the potency of the drug in binding to the receptor. The lower the value, the higher the potency for the receptor.

apparent that none of the SNRIs, SSRIs or NARIs shows any affinity for the α - or β -adrenoceptors, the dopamine 2 (D_2 -) receptor or the serotonin receptors, in contrast to the corresponding TCAs which have affinity for many of these receptor subtypes.

In contrast to the relative lack of effect of the second-generation antidepressants on the main neurotransmitter receptors implicated in depression, these drugs have a marked effect on the transporters for noradrenaline and serotonin in brain tissue. This is shown in *Table 14*.

Table 14

Inhibitory potency and relative selectivity of some antidepressants on monoamine uptake into brain tissue in vitro.

	Potency (nmol/L)		
	Inhibition of [3 H]5-HT uptake	Inhibition of [3 H]noradrenaline uptake	Inhibition of [3 H]serotonin uptake
SSRIs			
Fluoxetine	25	500	20
Sertraline	7.3	1400	190
SNRI			
Venlafaxine	39	213	5.4
NARI			
Reboxetine	1070	8.2	0.007
TCAs			
Amitriptyline	87	80	0.9
Clomipramine	7.4	100	13

Values greater than 500 nmol/L imply that the drug would have no effect on the functional activity of the transporter in vivo.

There are several classes of antidepressants that enhance noradrenergic function in the brain, but currently only the selective NARI, reboxetine, does so without affecting other uptake sites or neurotransmitter receptors. For example, the TCAs with a secondary amine side chain, such as desipramine, nortriptyline and protriptyline, and the modified TCA, maprotiline, show selectivity in inhibiting the noradrenaline transporter. However, their anticholinergic and cardiotoxic side-effects limit their use in many patients. Similarly the tetracyclic antidepressants, mianserin and mirtazapine, facilitate noradrenaline release by blocking the inhibitory presynaptic α_2 -adrenoceptors. However, these drugs also act on a number of serotonin receptors (5HT_{1A}, 5HT₂, 5HT₃). Of the cyclic antidepressants that are selective inhibitors of noradrenaline uptake, which include a number of drugs still in development (for example, tandamine, pirandamine, fluparoxan, talsupram and prindamine), only reboxetine has been marketed. In experimental studies, reboxetine has been shown to enhance noradrenaline release, presumably in blocking the inhibitory presynaptic α_2 -receptors slightly, and to block noradrenaline reuptake selectively.

Reboxetine has been shown to be effective in several standard acute in vivo models used to detect antidepressant activity (such as the reversal of reserpine- and clonidine- induced hypothermia), and in the olfactory bulbectomized rat model of depression which is only sensitive to the antidepressant action of drugs after chronic administration. Reboxetine, like most effective antidepressants, was also shown to decrease the density of cortical β -adrenoceptors after chronic administration. A summary of the mechanism of action of reboxetine is shown in *Figure 11*.

In clinical studies, reboxetine has been shown to be an effective antidepressant in double-blind and placebo-controlled trials and to be equally effective with TCAs and some second-generation antidepressants. Any drug that selectively enhances noradrenergic function would be expected also to increase the peripheral sympathetic drive, which may cause an increase in blood pressure. Although acute healthy volunteer studies revealed slight increases in blood pressure, in short and long-term clinical studies changes in blood pressure were no more common on reboxetine than placebo. The heart rate was slightly increased after reboxetine but desipramine

had a more pronounced effect in increasing the heart rate when given to the volunteers in therapeutic doses (50–100 mg). In addition, reboxetine and desipramine shortened the recovery time of the light reflex response; these effects are consistent with the sympathomimetic effects of the drug, which are a consequence of the inhibition of noradrenaline reuptake inhibition. The slight reduction in the salivary volume found in these clinical studies probably reflects the enhancement of the noradrenaline-induced inhibition

of central parasympathetic nuclei which follows the reduction in noradrenaline reuptake.

Summary

Reboxetine is the first of a series of NARI antidepressants which, in clinical trials, have been shown to be as effective as the TCAs and SSRIs, possibly with a reduced burden of side-effects and improved tolerability. Such drugs provide valuable tools for research into the role of noradrenaline in depression and help to extend the treatment of those depressed patients with low motivation and drive.

Extending the clinical use of antidepressants



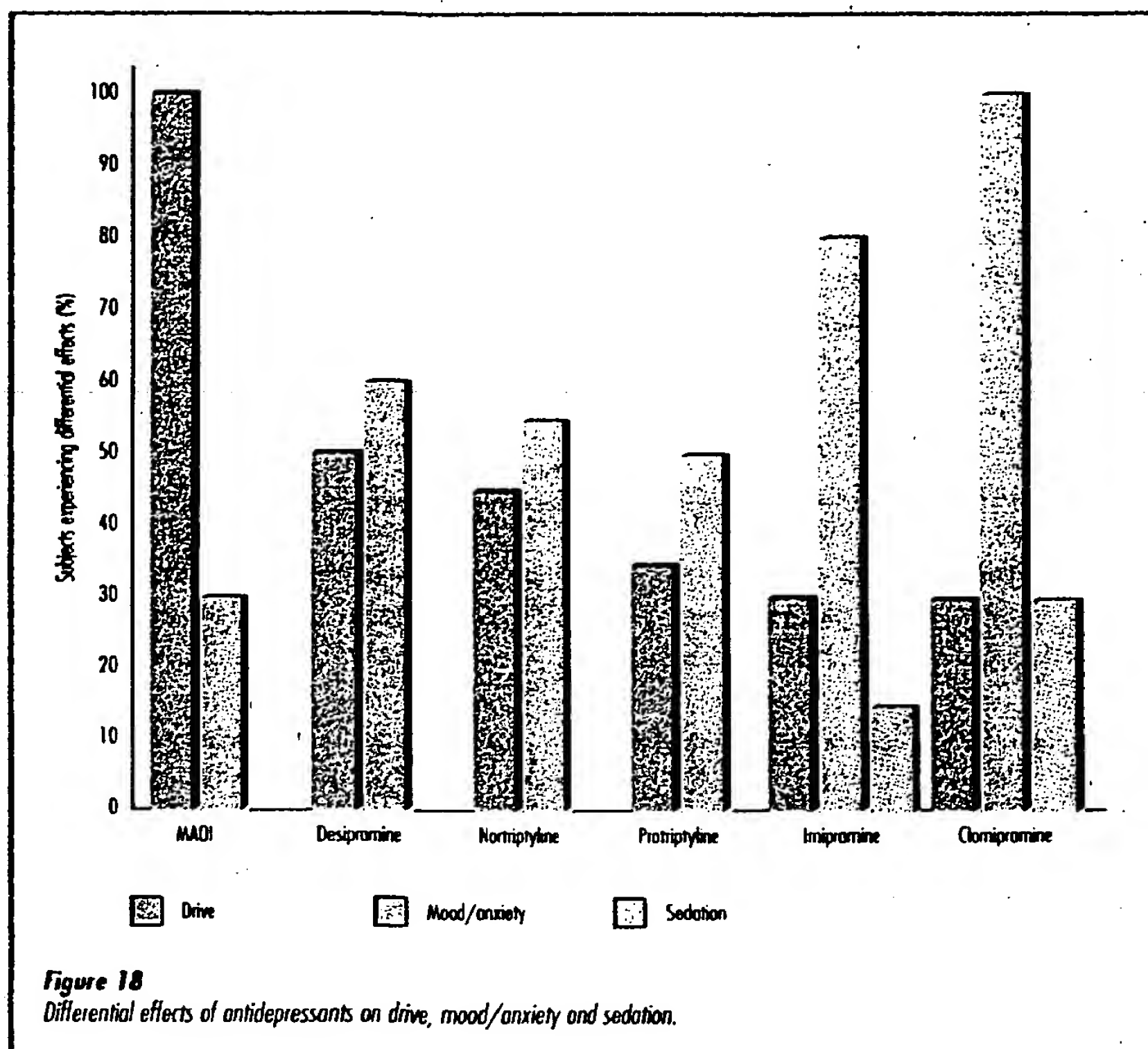
It is a mistake to regard all antidepressants as the same, that is, effectively as equivalent magic bullets. The original TCAs embodied a number of therapeutic principles to the point where, if re-launched today, drugs such as imipramine, desipramine, clomipramine, trimipramine and opipramol would be classified as belonging to different groups: SNRIs, NARIs, SSRIs, noradenergic and specific serotonergic antidepressants (NASSAs) and others. The recognition of depressive disorders was poor in the 1950s, but the recognition and detection of other conditions such as obsessive-compulsive disorder, social phobia and panic disorder were even poorer. As a result, the early thymoretic (drive-enhancing) and thymoleptic (mood-seizing) agents, as they were called, became antidepressants almost by default. They were clearly different agents from the sedative anxiolytics of the barbiturate and benzodiazepine type.

Categorizing the TCAs and monoamine oxidase inhibitors (MAOIs) simply as antidepressants was probably facilitated by the emergence of the monoamine hypotheses with their assumption of some final common biological lesion that underpinned depressive disorders. It was also facilitated by the standardization of clinical trials methodology, which took place at the end of the 1960s. Before that, the assessment of treatment effects depended primarily on clinical global impressions, which were that the antidepressants differed. In fact it was these impressions that led to the development of the SSRIs. Paul Kielholz from Basel produced a representative outline of clinical impressions in the late 1960s (see *Chapter 2*) (*Figure 18*).

Arvid Carlsson, was struck by the fact that the drive-enhancing agents were active on catecholamine systems whereas those that acted on a mood component were more likely to inhibit serotonin (5HT) reuptake. It was from these observed differences that the SSRIs were developed. The initial hope was that selective 5HT agents would be more effective, act quicker and have fewer side-effects than the older, less selective agents. This is clearly not the case.

From the vantage point of the late 1990s, as mentioned in *Chapter 1*, one way to characterize the therapeutic principle embodied in the SSRIs is in terms of a broad-ranging antinervousness principle – a non-sedative anxiolytic. Other possibilities are outlined in *Chapter 7*. This broad antinervousness action has an obvious use in depressive disorders, social phobia, obsessive-compulsive disorders, panic disorders and a range of other states. The first clear proof for it came with the discovery that clomipramine was more effective in the treatment of obsessive-compulsive disorders than imipramine. Subsequent trials have indicated that desipramine is virtually ineffective in obsessive-compulsive disorders. These observations led to the use of SSRIs for obsessive-compulsive disorders. In general drugs that have actions on the serotonergic system seem to be of use in these disorders, whereas drugs selective for noradrenergic systems do not.

Initially, it was argued that the responsiveness of conditions such as obsessive-compulsive disorders to antidepressants stemmed from the fact that a depressive disorder underlay these neurotic conditions; clearing up the depression would



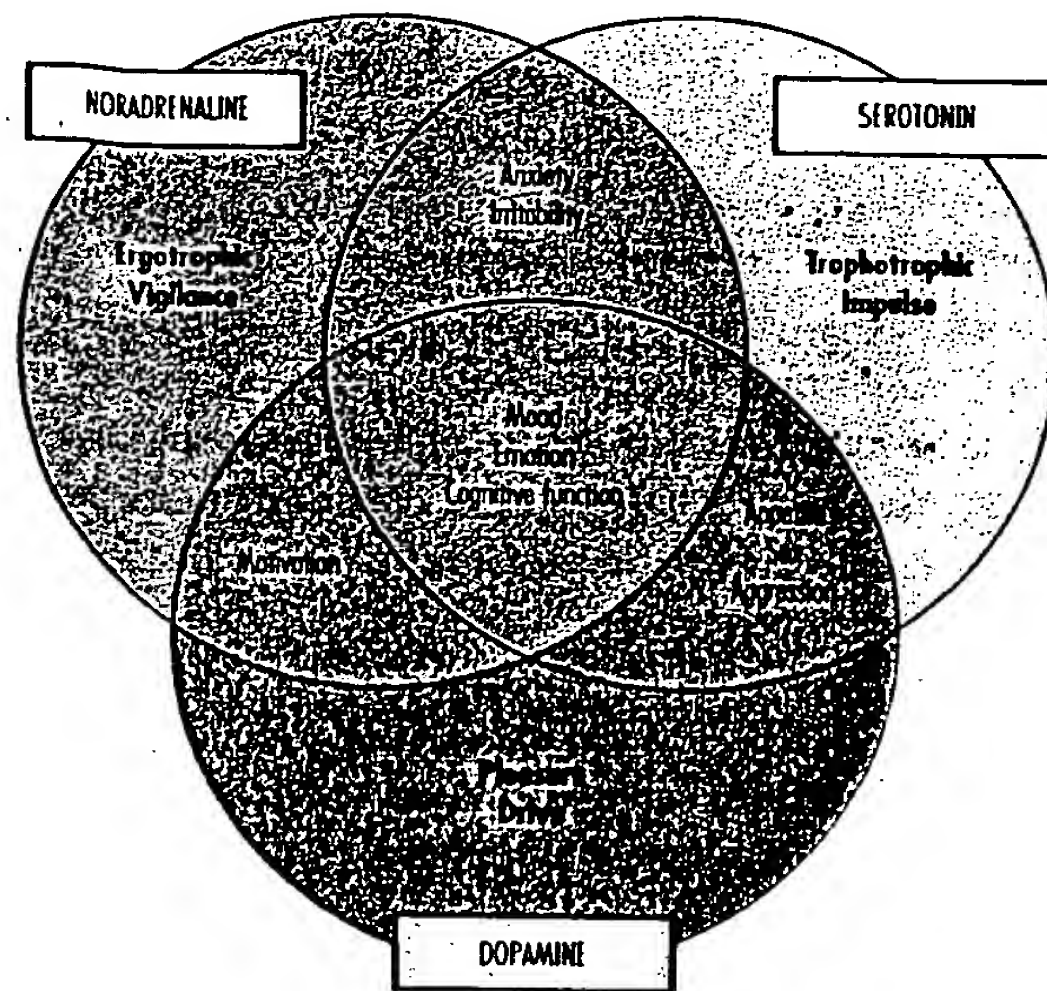
lead to an improvement in the neurosis. This is clearly not the case. The licences given to a number of the SSRIs for use in panic disorders, obsessive-compulsive

disorders and social phobia depend on a demonstration of effectiveness after exclusion of depression.

In recent years the focus on the SSRIs has helped to clarify the nature of their effects. There has, however, been neglect of the profile of action of drugs selective for noradrenergic systems. Agents that are active on noradrenergic systems seem, in the main, to be better at enhancing vigilance, drive and motivation, a profile of action that clearly benefits people with

depressive disorders (*Figure 19*). It may also be useful in panic disorders – where, for example, lofepramine has been shown to be effective. The use of MAOIs in social phobias also supports the idea that an action on catecholamine systems could also offer distinctly useful effects in these conditions.

Figure 19
Neurotransmitters and
behavioural functions



Currently drugs that are selective for noradrenergic systems appear to be more beneficial in severe types of depression, as well as in those that are characterized by psychomotor retardation and obvious complaints of fatigue, in addition to a loss of interest or pleasure in normal activities – the patient who is tired all the time. It is tempting to think that greater effectiveness in melancholic or severe types of depression is the same as a greater antidepressant potency, but this is not so. Antidepressant potency is somewhat mythical. The size of treatment effect for all these agents varies with the population being studied, whether they are young or elderly people, or whether they are anergic or anxious. Some of the SSRIs have been of use in a psychotic condition called body dysmorphic disorder; this indicates that they are not 'weaker' than the TCAs or agents selective for noradrenergic systems.

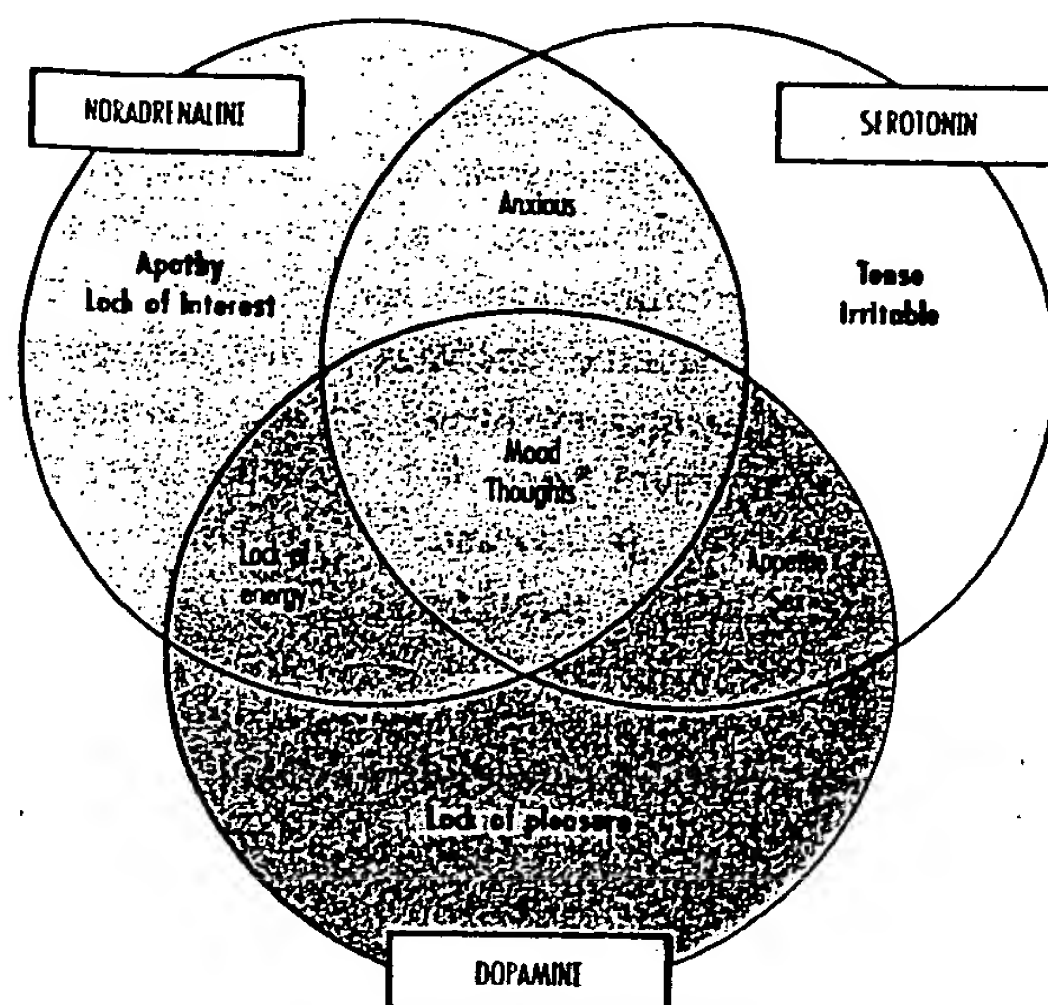
Based on strong indications that agents with actions on the noradrenergic system improve depressive states characterized by fatigue or anhedonia, it could be predicted that these agents would have benefits in chronic fatigue states, in addition to their usefulness in depressive disorders. To date the SSRIs have demon-

strated no such benefit. An explanation could be that some personalities are predisposed to showing signs of tiredness rather than anxiety when depressed, whereas others develop signs of anxiety.

It will be interesting to see in the future whether agents that are vigilant and drive enhancing, such as reboxetine, are of benefit to a variety of chronic fatigue syndromes as well as to conditions such as neurasthenia (*Figure 20*). Whether there are differential effects with patients who are more typically anxious being more likely to respond to a serotonergic agent remains to be seen.

Another group of patients who deserve further investigation are those who have conditions ranging from hypochondriasis to somatization disorders. To date little work has been done in this area, although these patients and those with chronic pain syndromes use up a good deal of the time and resources of general practice. The effects of noradrenergic agents in enhancing vigilance are relevant when dealing with the external environment, but the main noradrenergic nucleus, the locus coeruleus, has more extensive inputs from the internal than from the external environment. This can be demonstrated when

Figure 20
Neurotransmitters and
clinical symptoms.



we consider how a full bladder or bowel will override our interest in a lecture on pharmacology. A possible use for noradrenergic agents could then be predicted in conditions that have prominent somatic complaints.

Personality considerations may dictate the usefulness of noradrenergic-selective agents

in some conditions and of serotonergic-selective agents in others. Selective effects of this sort may help to open up the hitherto relatively neglected area of liaison psychiatry. In fact, maprotiline, a noradrenergic-selective agent, that is by far the best-selling antidepressant in Japan, sells particularly well in areas of psychosomatic medicine.

Other conditions

One way in which the action of serotonergic-active drugs can be characterized is in terms of a broad, non-sedative, antinervousness action, which underlies their use in a range of conditions. Just as morphine may have antitussive, analgesic, euphoriant and sedative effects, depending on which brain regions it acts on, so the SSRIs and noradrenergic-selective agents can also have more than one therapeutic functional effect.

The 5HT system was initially characterized as the trophotrophic or vegetative system. It is clear that the 5HT_{2C}-receptor is centrally involved in the regulation of aspects of dysphoria, on the one hand, and appetite, on the other, whereas 5HT_{2A}-receptors act on the slow wave components of sleep. The modulatory effects of 5HT availability as a consequence of fluoxetine use, for example, acting on 5HT_{2C}-receptors, possibly underlies the benefit of these agents in eating disorders. Fluoxetine, in particular, has been shown to have an appetite-regulating effect which appears to be beneficial in some patients. The effects of trazodone, mianserin, mirtazapine and nefazodone on 5HT_{2A}-receptors in practice has led to

some use of these agents to improve sleep quality, especially in the elderly.

One of the prominent effects (side-effect) of the SSRIs is their impact on sexual functioning; they are believed to produce sexual dysfunction, which involves delayed orgasm for both men and women. In a significant proportion of men, however, such effects have the potential to be therapeutically beneficial. There are estimates that up to one-third of men have premature ejaculation. Controlled trials comparing the use of clomipramine and placebo in premature ejaculation have indicated a clear use for the drug, with ejaculation being delayed significantly by use of 10–25 mg clomipramine 2–3 hours before intercourse. In a more recent trial comparing paroxetine with placebo, it was also found that the length of time to ejaculation was significantly extended in men with premature ejaculation.

In contrast antagonists at 5HT_{2A}-receptor sites could be expected to enhance orgasm, and such agents include the antidepressants trazodone and nefazodone. They could be considered to have a mild aphrodisiac effect, in terms of increasing sexual interest in both men and women. For men with premature ejaculation this could be a

problem. It could, however, be more useful for men or women who suffer loss of libido; it can also be used to manage sexual dysfunction induced by SSRIs. Buspirone, which acts as a 5HT_{1A}-agonist, appears to have similar effects, yohimbine, which acts on 5HT_{2A}-receptors, also has these effects.

Currently the effects of noradrenergic-selective agents on sexual functioning are not clear, and it is not known whether they have a therapeutic use.

Antidepressants have been used for a long time in chronic pain syndromes: their effectiveness has in fact led to the argument, by some investigators, that many pain syndromes are cases of masked depression. The development of the SSRIs has made it possible to explore this area more thoroughly. The relative inefficacy of the SSRIs in this area, when compared with desipramine and amitriptyline, would suggest that it is the TCAs' noradrenergic component that underpinned their use in pain syndromes. These issues could possibly be clarified by further studies with reboxetine.

Noradrenergic-selective agents, such as desipramine, are used widely in the USA for hyperactivity disorders in place of

agents such as methylphenidate. This use is entirely rational if the vigilance-enhancing properties of these agents are borne in mind. Desipramine is, however, a dangerous agent in overdose and its use is therefore problematic, for children. Studies of lofepramine and reboxetine are needed.

The SSRIs have shown a greater use in the treatment of premenstrual dysphoric disorder (PMDD) than the older non-selective TCAs. Trials with selective NARIs provide an opportunity to confirm whether the selective effect of 5HT agents in PMDD arises by virtue of their general anti-irritability profile of action or because of some other action related specifically to 5HT. Alternatively it is possible that any antidepressant would work quicker in PMDD, which is brief and reactive by nature; this could be because downstream effects do not build up in these conditions as they do in chronic depressive disorders. The drawback of the older non-selective agents could have been their weight-gaining side-effects rather than any lack of effect on the condition. This point may be clarified by trials with reboxetine in PMDD.

A use of SSRIs that is not widely known is in the treatment of cataplexy. An SSRI can

be used for cataplexy itself or when it is part of the narcoleptic syndrome.

The idea of noradrenergic and serotonergic types of depression has arisen from evidence that certain individuals respond better to serotonergic-selective agents and others respond to agents that act on catecholamine systems. There has been no experimental support for this idea. The work of Peter Joyce and colleagues suggests that patients with particular personality types are more likely to respond to selective noradrenergic or serotonergic agents, which may be a result of biological components of personality rather than of the depression itself. Noradrenergic personalities may be more likely to be easily tired and serotonergic personalities show greater irritability and impulsivity. Alternatively certain personality types may respond preferentially to the induction of sanguinity by serotonergic-selective agents whereas others respond better to the activating or vitality-restoring effects of noradrenergic-active agents. One way of ascertaining this is to ask patients whether the treatment suits them – does it offer them what they want from treatment?

A general rule of thumb

To date there has been a tendency in psychiatry and primary care to assume that antidepressants get patients well by simply raising monoamine levels. No-one has asked the question: what do we want treatment to do in order to get the patient well? This is in marked contrast to the treatment of cardiac, gastrointestinal or hypertensive conditions, where physicians usually have a clear view of what they expect from the treatment – for example, reduction in acid levels or killing off *Helicobacter pylori*, for gastrointestinal conditions.

The differences emerging between drugs that select different systems are forcing clinicians to confront this functional question. This makes the decision to prescribe more reflective, but it also offers greater chances of picking the right treatment. It should be possible to involve patients in this exercise by asking them what they think needs to be done in order to get them well. Do they say 'Make me energetic and more outgoing' or 'Make me less irritable and less anxious'.



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Research report

The clinical pharmacologic profile of reboxetine: does it involve the putative neurobiological substrates of wellbeing?

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Abstract

Following a review of the clinical trials of reboxetine, a new nonadrenergic reuptake inhibitor antidepressant, this paper presents a heuristic theoretical framework to better understand selective antidepressant action. For over three decades, the dominant views of antidepressant action have seen these agents active across all constitutional types and regardless of social setting. An increasing number of studies using quality of life methods are at odds with this view. This paper summarizes several of these studies, along with two studies of the effects of reboxetine on the quality of life, which reveal differential effects of selective agents that demand alternative explanations to the conventional monoamine theories. The authors submit that any revisions in our understanding of what is happening will have to pay attention to temperamental inputs that antedate affective episodes and to the sense of wellbeing and level of residual symptoms patients have on treatment after the acute phase of their illness has remitted. Obviously much more research needs to be done in this area. This invited paper sketches out, in very general terms, some provocative possibilities of how future understanding of antidepressants, temperament and their neurobiologic substrates could lead to better matching of specific antidepressants to specific temperament types. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Antidepressant; Reboxetine; Monoamine theories; Temperament; Quality of life

1. Introduction

In the mid 1960s, Paul Kielholz surveying the then available antidepressants, suggested that some depressed individuals get well by enhancing drive, while others help by doing something else which was

either more mood enhancing or more anxiolytic (Kielholz, 1968; Healy, 1997). The implication was that the range of different antidepressants embodied a number of different therapeutic principles. Two important developments supervened which tended to obscure the recognition of possible differences. One was the emergence of the monoamine theories of depression (Schildkraut, 1965; Bunney and Davis, 1965), which posited a common catecholamine lesion in mood disorders, which all antidepressants,

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regardless of their therapeutic class, acted to correct. The second was the adoption of rating scales such as the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory, reinforcing the impression that one was measuring the specific symptoms of a discrete disorder or disease entity (Healy, 1998a).

The catecholamine hypothesis was quickly complemented by an indoleamine hypothesis (Coppen, 1967 and 1972). This gave rise to the possibility that there might be catecholaminergic and serotonergic depressions. This issue was investigated extensively through the 1970s and early 1980s without a clearcut conclusion (Maas et al., 1984). Subsequent work with tryptophan-depletion and AMPT-challenge paradigms, however, has pointed to distinctive roles for the catecholamine and serotonin systems in mood disorders (Delgado et al., 1991 and 1993). This body of work has generally been interpreted in terms of discrete monoamine lesions, despite the fact that evidence of biochemical differences between subjects and differential responses to antidepressants might just as well stem from temperamental differences between subjects. Also consistent with a temperamental view of mood disorders, Delgado and colleagues have noted that their findings may speak primarily to a role for catecholamines or serotonin in the action of selective antidepressants rather than as evidence of a monoamine lesion.

Faced with Kielholz's schema, Arvid Carlsson suggested that those agents which were drive enhancing had preferential actions on catecholamine systems and those that were doing something else acted on the serotonin (5HT) system (Carlsson et al., 1969; Carlsson, 1996). This insight ultimately led to the creation of the 5HT Reuptake Inhibitors (SSRIs), of which zimelidine, in 1971, was the first patented and indalpine, in 1978, was the first released into clinical use. A subsequent generation of SSRIs came into clinical practice from about the mid-1980s. Despite the fact that the SSRIs were only developed because antidepressants differed in their functional effects and although they embodied a selective therapeutic principle, the dominant views of the day continued to see all antidepressants as somehow acting on some final common pathway. From 1975 through to 1985, this was beta adrenoceptor downregulation (Verulani et al., 1996), while more

recently the focus has been on 5HT-1a receptors (Artigas et al., 1994). Functional differences between the SSRIs and other antidepressants, on either a physiological or on a behavioral level, have been ignored in favour of views which emphasize cross-talk between monoamine systems (Manier et al., 1984).

Clinically, the SSRIs were quickly compared with the tricyclic antidepressants (TCAs) from the points of view of safety in overdose and freedom from side-effects, such as excess sedation and weight gain. This profile of effects made them more suitable for wider use in primary care depressive disorders than the TCAs had been. The area of primary care mood disorders, which almost certainly embraces a range of conditions, in which there are varying pharmacogenetic, temperamental and psychosocial inputs, provides possibilities for investigations with antidepressants of different pharmacological profiles. To date, these possibilities have not been addressed, owing in part to the side-effect profile of the older TCAs. The emergence of a selective norepinephrine reuptake inhibitor, reboxetine, which is neither sedative nor associated with weight gain and which is safe in overdose (Montgomery, 1997), might help us obviate some of these problems. It is now, in principle, possible to begin to examine the effects of different therapeutic interventions against a background of differing temperament types, different pharmacogenetic profiles and different comorbidities, in a way that has been impossible hitherto.

2. Reboxetine: pharmacological profile

Reboxetine is a selective norepinephrine reuptake inhibitor derived from viloxazine. Unlike previous norepinephrine reuptake inhibitors, clesipramine, maprotiline and lofepramine, it has no significant effects on histaminic or cholinergic receptors or on adrenergic receptors other than the norepinephrine reuptake site (Brunello and Racagni, 1998).

In animal studies the potential antidepressant activity of reboxetine was first brought to light in the 1980s by its antagonism of reserpine-induced hypothermia and blepharospasm (Melloni et al., 1984), as well as antagonism of clonidine-induced hypothermia (Melloni et al., 1984). Indeed its antagonism of

clonidine-induced hypothermia was more rapid than that with available tricyclic antidepressants, suggesting that it might have a faster rate of onset than other antidepressants; it prevented clonidine-induced hypothermia after a single dose, where chronic dosing was needed with the tricyclic antidepressants.

Reboxetine appears to be devoid of significant inhibitory effects on common cytochrome P450 enzyme systems (Dostert et al., 1997). In humans, its half life is approximately 13 h, permitting single daily dosage, although it has been studied in clinical trials in a b.i.d regime. Unlike the tricyclic antidepressants, the recommended dose 8 mg per day can be given on initiating therapy. The drug, therefore, appears suitable for use in primary care by virtue of its dose regimen and its low liability for drug–drug interactions. It is also potentially suitable for use in combination with other psychotropic agents, by virtue of its lack of 5HT-reuptake inhibiting properties as well as the lack of significant monoamine-oxidase inhibiting properties (Dostert et al., 1997; Brunello and Racagni, 1998).

2.1. *Reboxetine: clinical trials*

Short term controlled clinical trials with reboxetine have been conducted against placebo, desipramine (150–200 mg/day), imipramine (150–200 mg/day) and fluoxetine (20–40 mg/day) (Montgomery, 1997). Inpatients or outpatients with a diagnosis of major depressive disorder according to DSM-III or DSM-III-R (APA, 1980; 1987) have entered a total of eight randomised double-blind clinical trials with reboxetine (8–10 mg per day in adults or 4–6 mg per day in the elderly) versus other agents. The Hamilton Depression Rating Scale (Hamilton, 1960) was used as the primary measure of efficacy. Other measures included the Montgomery Asberg Depression Rating Scales (Montgomery and Asberg, 1979) and a Clinical Global Impression Scale (Guy, 1976), as well as a patient self-assessment measure of social functioning, the Social Adaptation Self-Evaluation Scale (SASS) (Bosc et al., 1997) which was used in the two fluoxetine-controlled studies.

The SASS is a 20-item questionnaire, taking 5 min to complete, which was developed on the basis that a drug active on catecholamine systems might show

greater effects in areas of motivation than a drug active on 5HT systems (Dubini et al., 1997; Bosc et al., 1997). The SASS derives originally from assessments of social functioning by Myrna Weissman and Eugene Paykel in the mid-1970s, which led to the development of a social adjustment scale (SAS) (Weissman et al., 1974; Weissman, 1997). The original Weissman-Paykel approach involved observer-based assessments of social functioning. Assessing the area of social adjustment/social function through self-report produces a scale that overlaps heavily with many quality of life scales. This area is clearly of importance as there are indications that patient perceptions of well being as assessed by quality of life measurements may predict the stability of clinical response in the longer term (Thunedborg et al., 1995). The SASS was validated in French samples. While Danish, Finnish, English and Spanish versions now exist, it remains to be established that these translated versions possess the same psychometric properties and validity when applied to a range of populations of varying ethnic and cultural backgrounds.

Two short-term double blind studies compared reboxetine to placebo in acute depression in both inpatients and outpatients between the ages of 18 and 65 and in both instances reboxetine was clearly superior (Montgomery, 1997). A study comparing reboxetine and imipramine in adult patients found a significantly greater response rate with reboxetine than with imipramine with a significantly lower frequency of anticholinergic, sedative and cardiovascular adverse events in the reboxetine group (Berzowski et al., 1997). A study comparing reboxetine with imipramine in the elderly showed similar response rates with both active drugs and fewer adverse events with potentially serious consequences in the reboxetine group (Mucci, 1997).

Two short-term studies were conducted comparing reboxetine and fluoxetine, one of which contained a placebo arm. Using observer-rated disease specific instruments, such as the HDRS, both active drugs proved equivalent to each other and in the placebo controlled study, they both proved superior to placebo (Montgomery, 1997; Massana et al., in press; Healy, 1998a; 1998b). A further trial compared reboxetine with desipramine and placebo, in which reboxetine proved superior to placebo where

desipramine did not (Ban et al., 1998). In a long-term placebo-controlled study of 283 patients on either reboxetine or placebo, followed up over a 12-month period, it was found that there was a significantly lower rate of relapse on reboxetine compared to placebo (Montgomery, 1997).

Using placebo-controlled studies to define reboxetine's tolerability profile, the most common adverse events associated with its use have been dry mouth, constipation, sweating and insomnia. The occurrence

of some 'anticholinergic'-type side-effects may reflect reboxetine's central noradnergic reuptake inhibition (Szabadi et al., 1998). Serotonergic-type side effects were no more common on reboxetine than on placebo. In clinical trials, reboxetine had minimal effects on the cardiovascular system and early clinical experience suggests a low toxicity in overdose (Baldwin et al., 1998).

In order to test for differential effects between norepinephrine selective and serotonin selective agents, the SASS was incorporated in the two short-term reboxetine-fluoxetine studies. In the placebo-controlled study, both active agents produced significantly greater improvements in social functioning than placebo on SASS scores (Fig. 1; Dubini et al., 1997). The reboxetine results at last assessment were in addition significantly better than the fluoxetine results both in the overall group (Fig. 2) and in those who were defined as responders (Fig. 3) according to a HDRS criterion ($\text{HDRS} \leq 10$). In the overall group, reboxetine was significantly superior to placebo on all items of the scale and superior to fluoxetine on nine items of the scale. In those defined as responders, reboxetine was superior to fluoxetine on 14 of the 20 items on the scale. A second study, which directly compared reboxetine and fluoxetine

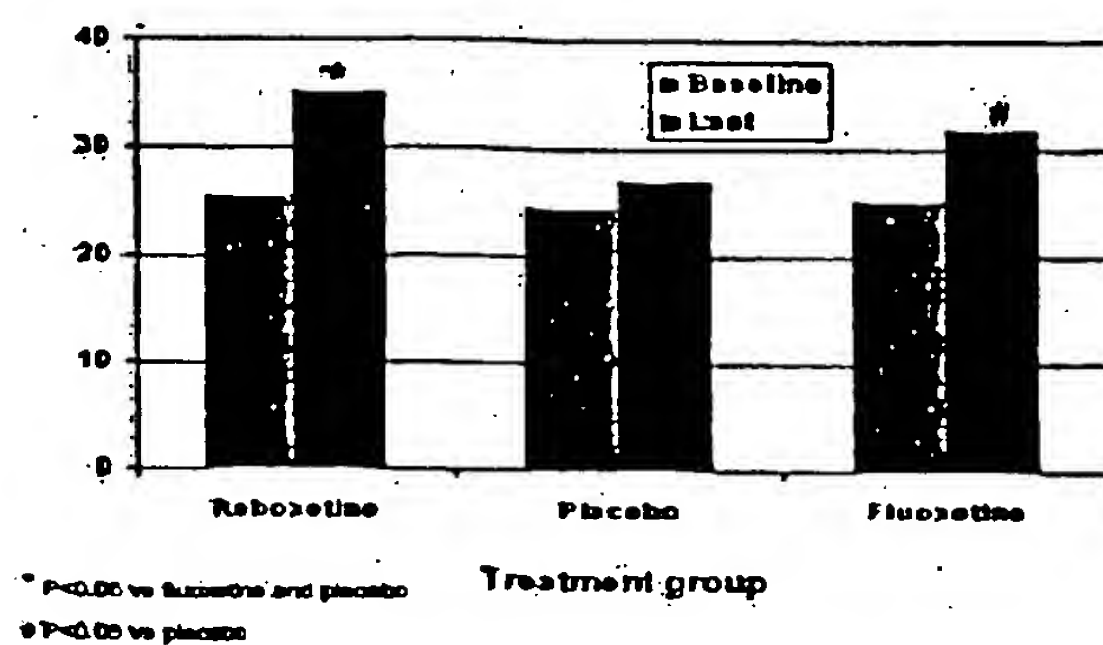


Fig. 1. SASS total score: mean values at baseline and at last assessment in the reboxetine, placebo and fluoxetine groups.

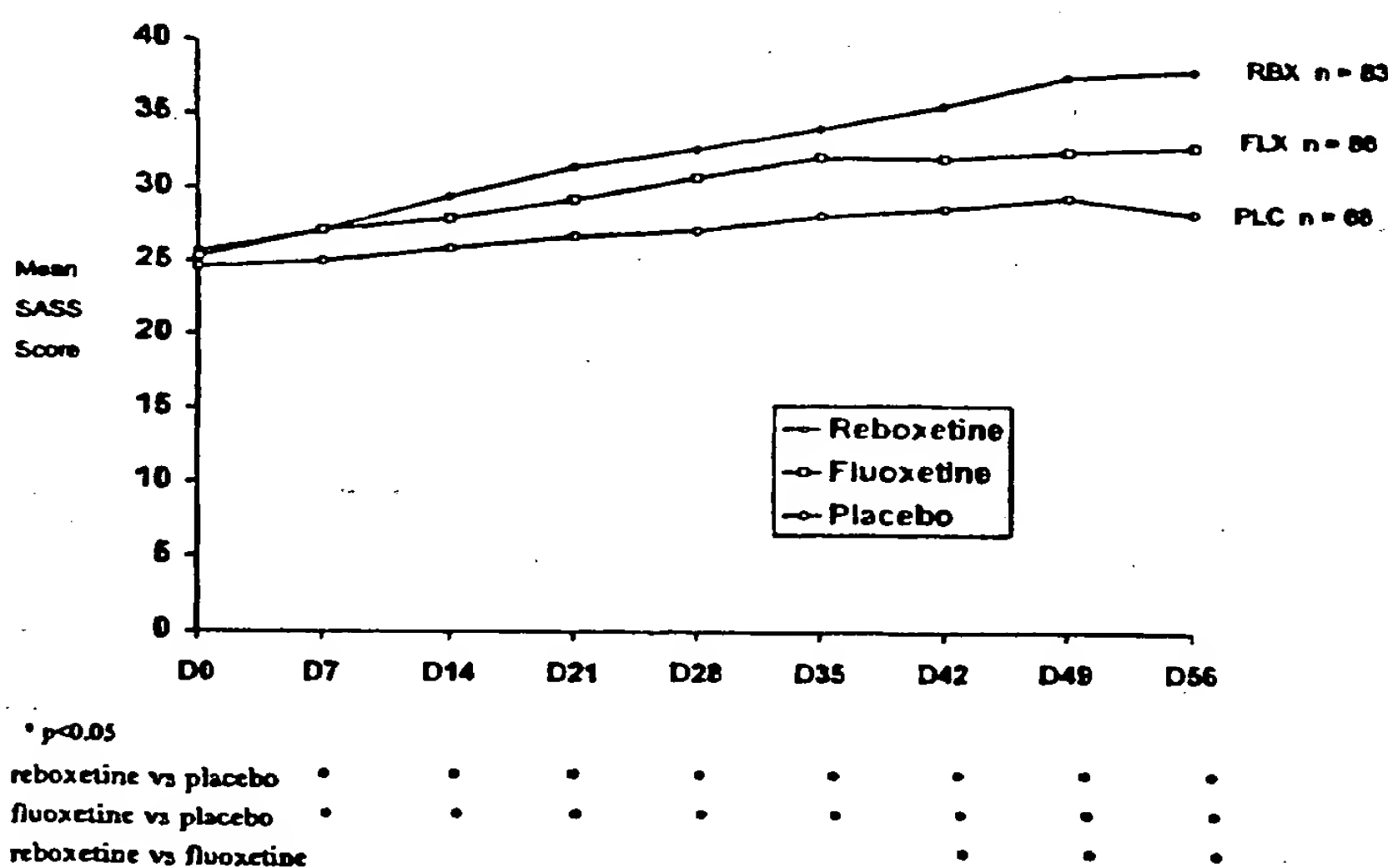


Fig. 2. SASS scores: overall population.

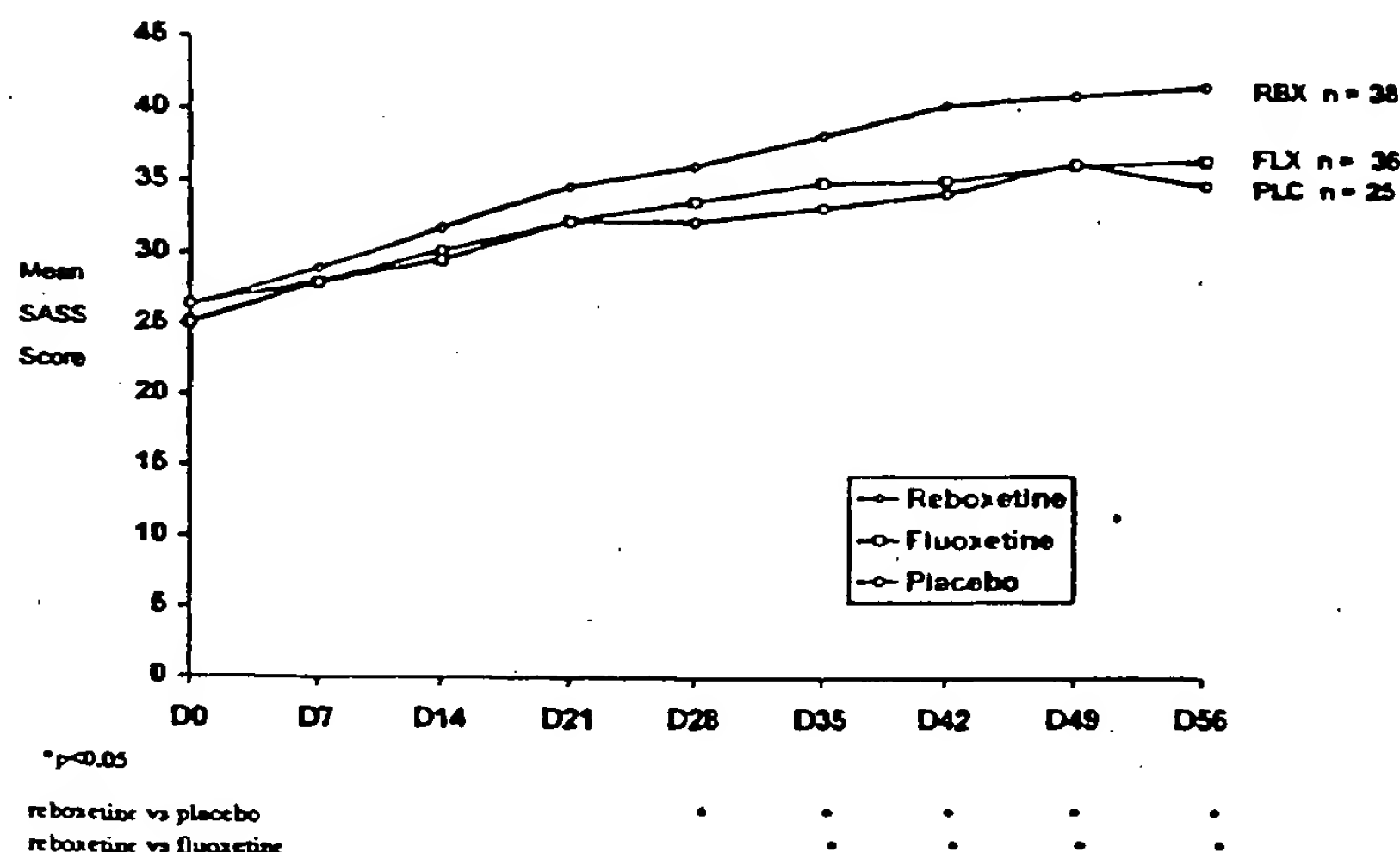


Fig. 3. SASS scores: patients in remission.

gave similar results (Massana et al., in press). Reboxetine was associated with a return to SASS scores in the normal range (35–52), whereas fluoxetine was not (Figs. 2 and 3). Taking the responder group only, the mean figures translate as follows: over three-quarters of those defined as well by the HDRS defined themselves as well on the SASS, whereas less than two-thirds of those taking fluoxetine and defined as well on the HDRS defined themselves as well on the SASS (Fig. 3). These differences between the drugs do not appear to stem from a differential efficacy, at least as conventionally defined, as HDRS scores were similar for both groups (Fig. 4).

2.2. Discussion

These results from clinical trials, in conjunction with the results of preclinical studies, strongly suggest that reboxetine is an agent possessing antidepressant properties with a treatment effect size in the range of standard antidepressants and a favorable pharmacogenetic and tolerability profile. The differential effects of reboxetine and fluoxetine on the SASS have a particular significance for the management of primary care mood disorders as reboxetine's comparative tolerability and safety means that, like

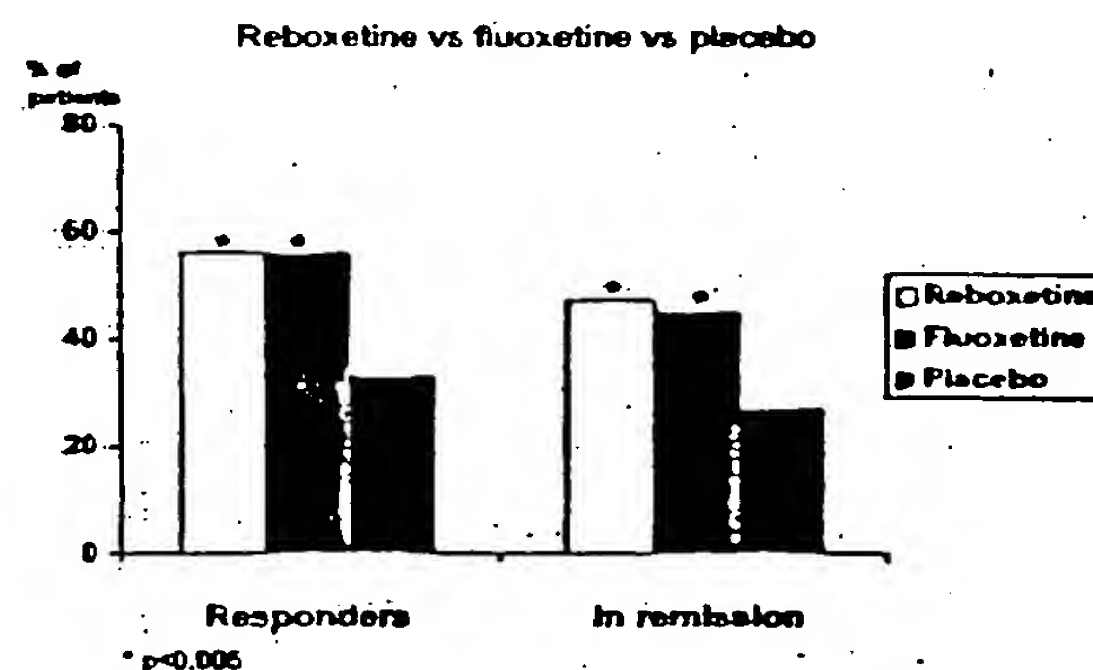


Fig. 4. Reboxetine versus fluoxetine: response to treatment.

fluoxetine, it is likely to be deployed most extensively in primary care settings.

The effects of reboxetine have implications for our notions of what antidepressants 'treat' in patients with mood disorders. They also yield indications for effects these agents have on how well patients feel when they have been restored to 'normal' that may have consequences for the longer-term management of these conditions. The discussion section of this paper will focus on what current data support on the issue of what antidepressants treat in patients with mood disorders. An additional more speculative

commentary section will tackle the second issue of wellbeing in the maintenance phase of treatment.

The demonstration that both selective norepinephrine uptake inhibitors and selective serotonergic reuptake inhibitors get primary care depressed patients well has implications for our notions of what antidepressants do. While there are some indications that drugs active on norepinephrine systems are more likely to benefit patients with classic melancholic features, such as loss of energy and loss of interest and to benefit more severely depressed patients (Nelson et al., 1984; Nelson and Mazure, 1990), the majority of mild to moderate primary care depressions, in the light of these results with reboxetine, *a priori* would appear to stand a roughly equal chance of having the core features of their disturbance ameliorated by a variety of different therapeutic agents. This is an argument against any common mechanism of action of the antidepressants. By extension, it suggests that whatever lesion or lesions there may be in depressive disorders, these do not lie in the monoamine systems on which the majority of antidepressants act.

There are a number of other features of antidepressant actions, which support such an interpretation. One is the fact that the SSRIs in particular have effects across a variety of conditions such as social phobia, obsessive compulsive disorder, panic disorder, body dysmorphic disorder and posttraumatic stress disorder (PTSD) in addition to mood disorders (Goodnick and Goldstein, 1998). Indeed their treatment effect sizes for these other conditions may be greater than the effect size in severe mood disorders. In contrast, while norepinephrine reuptake inhibitors are useful for depressive disorders and possibly panic disorder, they are likely to be useful for a different spectrum of disorders, including attention deficit hyperactivity disorder and pain syndromes (Leonard and Healy, 1998), than the SSRIs. A differential efficacy across a range of conditions suggests that these differing therapeutic principles produce distinctive functional changes. These functional changes have a modest therapeutic benefit across a range of quite different psychopathological syndromes rather than a large and specific therapeutic benefit for particular conditions (Healy, 1998b).

In the case of the SSRIs there is good evidence that these agents can produce a reduction in emotion-

al reactivity to stressors. The possible physiological underpinnings of this effect may involve a dampening action of 5HT on locus coeruleus reactivity to excitation. It has been shown that the excitatory effects of the main excitatory neurotransmitter, glutamate, on the locus coeruleus are blocked by 5HT (Aston-Jones et al., 1991; Svensson, 1997). This functional effect probably rather precisely underpins the role of SSRIs in dampening unwanted reactivity in PTSD. Behaviorally, such a physiological effect would be expressed in terms of increased sanguinity. This is the kind of effect that could be expected to have a modest utility across a range of conditions such as OCD, social phobia and panic disorder. An alternative is that the treatment effect size might be quite different in different personality types. Where an induction of sanguinity might be of benefit in all personality types in the case of PTSD, in the management of depression a dampening of responsiveness to the environment might be more welcome in some personality types, such as obsessives, than in others. The precise nature of the behavioral effect produced by norepinephrine reuptake inhibitors (NRI) remains to be specified clearly. A long tradition, stemming from Hess, of seeing the norepinephrine system as the 'ergotrophic' system suggests that NRIs act to facilitate behavioral output by enhancing social drive and motivation, as well as vigilance (Svensson, 1997; Healy and McMonagle, 1997).

Further clinical studies will be needed to tease apart some of the issues here. These will include studies of reboxetine across a range of other conditions such as OCD, social phobia and PTSD. Comparative studies of selective agents in depressions with comorbid personality disorders are also called for. Finally, it will be important to study reboxetine using a range of other quality of life and social functioning instruments.

3. Toward a new theoretical framework of antidepressant action

In addition to the effect of reboxetine on conventional indicators of antidepressant efficacy, the findings of differential effects between it and fluoxetine on the SASS attract discussion and comment. These

findings are of interest as differential effects of this type are rarely reported and as such were unexpected. A number of cautions are in order. First, it remains to be seen if these findings can be replicated with better known instruments such as the SF-36, which has been far more extensively used and whose psychometric properties have been explored in greater detail. Second the database from which conclusions can be drawn remains very small. For example, it will be important in due course to establish what contribution a differential burden of side-effects may have contributed to the picture revealed by the SASS findings but the current database is too small to permit a convincing analysis of this question. It is also important to note the SASS is a self-report scale. As such it is by no means clear that anything to do with objective social functioning is actually being measured when this instrument is used. Finally in so far as differential effects have been demonstrated in this study it is not clear that the effect is not a temporal rather than an absolute effect. With a longer observation period, there might be a closer approximation between the findings on both active drugs.

Despite these caveats, some speculation is called for, if only to enable the process of constructing experiments that might better exploit the opportunity opened up by these differential effects. These SASS results suggest that the HDRS failed to detect real differences between the two agents. In other words, while what are conventionally thought of as being core features of mood disorders, such as sleep and appetite disturbance, may improve on both drugs, other dimensions of the disturbances that are the affective disorders may not have returned to normal. Which dimensions?

One possibility takes us back to the way psychosyndromes and the effects of psychotropic drugs were viewed before the rise of the amine theories and the HDRS. This view is caught well in a quote from Horsley Gantt: "It is quite likely that in psychiatric diseases, the action of the drug is determined more by the type or temperament of the individual than by a clinical diagnosis or the disease symptomatology" (Gantt, 1967). In recent years, this alternative viewpoint has been most clearly expressed in the work of Akiskal (Akiskal, 1995; 1996). Current clinical trial methods, in contrast,

have focused almost exclusive attention on the supposed core features of a mood disorder, which had been thought to derive from an underlying monoamine lesion. This approach has neglected for over two decades temperamental inputs to mood disorders and the possibility that differing therapeutic principles may accordingly be differentially effective in different affective syndromes. A great deal of work has been done to determine whether there are noradrenergic or serotonergic depressions, with investigators seeking MHPG or DHPG markers supposedly of a noradrenergic lesion or 5HIAA markers of a serotonergic lesion (Maas et al., 1984). Had these been found and had they predicted the response to norepinephrine selective agents or serotonergic selective agents, however, there is an alternative interpretation of the outcomes that has been neglected. This is that noradrenergic and serotonergic indices may be markers for temperamental types rather than for physiological lesions.

Some indicators of a new way forward in this area have come recently from work by Farde et al. (1997) who radiolabelled D2 receptors in healthy volunteers and found both considerable variation in D2 receptor density but more importantly that this variation correlated with aspects of personality. This result has already been replicated (Breier et al., 1998). If this is true for D2 receptors, it is likely to be true for noradrenergic and serotonergic receptors. And if this is the case, one might predict quite different responses to norepinephrine or serotonin selective agents as a consequence. On this basis, one might predict that different constitutionally-based personality types would respond to different pharmacological interventions. This has been predicted by Akiskal (Akiskal, 1996; 1997). This perspective has also found some empirical support in a study by Joyce et al. (1994) who investigated the influence of temperamental types on response to norepinephrine and serotonin preferring antidepressants. These researchers randomised a group of patients attending hospital clinics and emergency departments to either desipramine or clomipramine. They made no attempt to exclude individuals with marked personality variations. They found that asthenic personality types responded better to desipramine while individuals with borderline personality features showed a better response to clomipramine. In severe cases, tem-

peramental type predicted up to 50% of the variance in responsiveness to the different antidepressants (Joyce et al., 1994).

These findings can be explained in a variety of ways that may potentially be teased out further using highly selective agents, such as reboxetine and citalopram. One possibility is that a direct physiological input to temperament may mean that selective agents may act preferentially on the temperamental input to a psychosyndrome and they may act to bring about a resolution of the syndrome by modulating the 'disorder' in the personality. An alternative is that certain temperament types may react either favorably or adversely, for example, to the sanguinity inducing effects of an SSRI.

On this latter point, two possibilities present themselves. One is that certain temperamental types, by virtue of different physiological inputs, may be more liable than others to profound reductions in emotional reactivity in response to an SSRI for instance, amounting to emotional blunting. Effects of this nature could potentially account for the differential effects between reboxetine and fluoxetine on the SASS. A second possibility is that, given comparable reductions in emotional reactivity, some temperamental types may react adversely to the impact of this effect on their overall psychological make up. All individuals with PTSD may appreciate this effect regardless of temperamental type, but for other conditions, for example, clinically depressed individuals with marked obsessional features may welcome the relief conferred by sanguinity, whereas these same effects may be quite unwelcome for the restless, novelty-seeking temperament types (Akiskal, personal communication, August, 1998).

The view of antidepressant actions proposed above suggests that actions on different monoamine systems may bring about a resolution of depressive disorders indirectly. This view is in line with a view recently expressed by Angst and colleagues: "The therapeutic qualities of antidepressants do not lie in the suppression of symptoms but rather are related to their ability to elicit or maintain certain conditions which allow recovery in a subgroup of patients who would otherwise remain non-responsive" (Stassen et al., 1997).

But, if this is the mode of action of the antidepressants, one can expect treatment to continue to exert

these effects on formerly depressed individuals, in much the way that the drug might be expected to work on healthy volunteers. The question then arises as to how much the vigilance or drive-enhancing effects of norepinephrine reuptake inhibitors might be likely to impact on daily functioning or a sense of wellbeing. This point is of considerable relevance to questions of remission and relapse in the case of antidepressant therapy. To date, advice has focused almost exclusively upon getting depressed patients on to antidepressant therapy and keeping them on the treatment in order to forestall relapse, without any great deal of consideration of whether the individual is on the correct antidepressant or not. It is clear, however, that a large number of depressed subjects following the relief of the core disturbances may remain with low-grade symptoms despite ongoing treatment. Furthermore, there are indications that a lack of wellbeing, following the resolution of the acute phase of the disturbance, as measured by quality of life (QoL) instruments, may predispose to future relapses or earlier recurrences of the disorder (Souetre et al., 1996; Lonquist et al., 1994; Thunelborg et al., 1995).

This area of wellbeing has been neglected in psychiatry/psychopharmacology to date. The neglect may stem in part from a fear that feeling well may herald a switch into mania. There are robust grounds to support a distinction between wellbeing and hypomania, however. The SASS, by virtue of its self-report character, has a great deal in common with QoL instruments and as such may best be interpreted as reflecting the sense of wellbeing subjects have while on treatment. The effects of reboxetine, as assessed by the SASS, may help shed further light on the interplay between temperament, pharmacogenetic and psychosocial factors in this area.

A recent study of social interactions in healthy volunteers taking paroxetine (Knutson et al., 1998) revealed a complex picture with volunteers reporting 'anxiolytic' effects but also appearing to observers to show more affiliative behavior. It is quite possible, therefore, that in certain individuals an SSRI may enhance aspects of social functioning, even though subjects record a reduced sense of wellbeing at the same time. In the populations studied with reboxetine, the most parsimonious interpretation at present

is that a greater proportion of subjects experienced a sense of wellbeing on reboxetine compared to those taking fluoxetine. Whether this translates into enhanced social functioning remains to be determined; bearing in mind that social functioning almost certainly has many different components which may vary independently. It, similarly, seems unlikely that feeling well on treatment is some unitary dimension that is produced equally by drugs with a particular pharmacological profile in all temperaments and social settings. The SASS data, however, suggests that there are some temperamental types who do feel better, or have a better quality of life, on norepinephrine selective agents. Further studies are needed to clarify this question. What is most crucial to the temperamental specificity question, is whether different antidepressants impact differentially on the range of social dysfunctions documented by Wells et al. (1989, 1992) generically for all common depressive subtypes.

We have offered here facts and speculations that pertain to the very nature of depression and its temperamental substrates. These are merely provocative possibilities for future research on the putative neurobiologic substrates of wellbeing. We submit that the recovery process in depression will be eventually much informed by such an approach.

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(57) **ABSTRACT**

A method and composition for transdermal delivery of pharmaceuticals or combinations of pharmaceuticals is provided. The pharmaceuticals are delivered using a matrix of a lecithin gel such as a lecithin organogel. A number of psychopharmaceuticals can be used including fluoxetine, sertraline, carbamazepine, paroxetine, amitriptyline, trazadone, venlafaxine, propranolol, bupropion, valproic acid, nefazodone, ketoprofen, gabapentin, piroxicam, doxepin, guaifenesin, pemoline and doxepin and combinations.

11 Claims, 1 Drawing Sheet

SP-SCMO Medication Management (CCH ver. 4-20-08) 90642.DOC

Patient _____ Date _____

Current Medications:

1)	_____
2)	_____
3)	_____
4)	_____
5)	_____
6)	_____

Diagnosis: Axis 1: _____ Axis 2: _____
Axis 3: _____ GAF: _____

Subjective _____

Objective : APPEARANCE
SPEECH
MENTOR
APETITE
CLINICAL RPH'S
SLEEP

AFFECT
CONCENTRATION
IRITABILITY
ANXIALITY
ENERGY LEVEL
WEIGHT

SIDE EFFECTS _____

RESPONSE OF DEPRESSION SYMPTOMS TO MEDICATIONS
EXCELLENT GOOD POOR N/A

RESPONSE OF ANXIETY SYMPTOMS TO MEDICATIONS
POORLY GOOD POOR N/A

CONCURRENT MEDICATION CONDITIONS _____

ASSESSMENT:

PLAN: 1) Continue med: _____
2) Change dose: _____
3) New Med _____
4) _____

LAB STUDIES ORDERED _____
OTHER: _____

cpt 90862 Medication Management (cdw ver. 4-24-95)

90862.DOC

Patient: _____ Date: _____

Current Medication: 1) _____
2) _____
3) _____
4) _____
5) _____
6) _____

Diagnoses: Axis 1: _____
Axis 2: _____ Axis 3: _____
GAF: _____

Subjective: _____

Objective :	APPEARANCE _____	AFFECT _____
	SPEECH _____	CONCENTRATION _____
	MEMORY _____	IRRITABILITY _____
	APPETITE _____	AV HALLUC. _____
	CRYING SPELLS _____	ENERGY LEVEL _____
	SLEEP _____	WEIGHT _____

SIDE EFFECTS: _____

RESPONSE OF DEPRESSION SYMPTOMS TO MEDICATIONS:

EXCELLENT	GOOD	FAIR	POOR	N/A
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RESPONSE OF ANXIETY SYMPTOMS TO MEDICATIONS:

EXCELLENT	GOOD	FAIR	POOR	N/A
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CONCURRENT MEDICATION CONDITIONS: _____

ASSESSMENT: _____

PLAN: 1) Continue meds: _____
2) Change dosage: _____
3) New Med: _____
4) _____

LAB STUDIES ORDERED: _____

OTHER: _____

Fig. 1

METHOD AND COMPOSITION FOR TRANSDERMAL ADMINISTRATION OF PHARMACOLOGIC AGENTS

The present application is a continuation-in-part of PCT/US97/19651 and of U.S. patent application Ser. No. 08/957,485, filed Oct. 24, 1997, now abandoned, which claims priority based on provisional application Ser. No. 60/029,120 filed Oct. 24, 1996.

The present invention is directed to transdermal administration of pharmacologic agents, and in particular to transdermal administration of drugs including antidepressant serotonin specific reuptake inhibitors (as SSRIs) such as fluoxetine, antidepressants such as bupropion and reboxetine, tricyclic antidepressant medications that have neuropathic pain treatment efficacy such as amitriptyline and doxepin, mood stabilizers such as carbamazepine, or valproic acid, Attention Deficit Hyperactivity Disorder (ADHD) medications such as pemoline anti-inflammatory or analgesic medications such as ketoprofen or piroxicam, treatments for impotence such as sildenafil and or anti-convulsants believed to possess neuropathic pain treatment efficacy such as gabapentin, carbamazepine, or combinations thereof such as using a gel matrix, preferably a lecithin organogel and/or a polymer gel.

BACKGROUND INFORMATION

In the past, patients suffering from a wide variety of conditions have been successfully treated by administration of pharmacologic agents. A vast majority of such patients receive doses of these agents orally. Unfortunately, in some situations, oral administration of such agents has been infeasible or ineffective. In some cases, oral administration is associated with side effects, particularly gastrointestinal side effects, sedation, or weight gain which cannot be tolerated well by the patient. In other cases, malabsorption of oral preparation have resulted in subtherapeutic plasma levels. In other cases, the agents have relatively short plasma half-lives, necessitating inconveniently frequent dosing. In general, oral delivery involves a time delay as the pharmaceutical is absorbed via the digestive system before entering the bloodstream. A number of agents which have traditionally been administered orally or by injection have been inappropriate or suboptimal for some patients when so-administered.

There are a number of medications which in at least some patients are not tolerated well when orally administered (e.g. which cause undesirable gastrointestinal or other side effects) and/or which provide undesirably high or low concentrations or delayed concentrations in a target tissue. In some cases, dosages which are appropriate for oral administration, upon being distributed more or less uniformly throughout the body, are undesirably low in a particular tissue to achieve desired results. Oral or injection administration may result in too slow or too rapid increase in blood plasma levels, e.g. may involve an undesirably long time delay as the pharmaceutical is absorbed by the digestive system before entering the bloodstream, or may result in a "spike" in blood plasma levels followed by an undesirably low level, where a more constant level would be preferable. Some pharmaceuticals are particularly prone to cause or contribute to liver damage when administered orally.

One alternative route of administration for selected pharmaceuticals, has been transdermal delivery. Transdermal delivery has been utilized, e.g., for the treatment of high blood pressure, for ischemic heart disease and for hormone replacement. Transdermal delivery is not necessarily appropriate for all types of pharmaceuticals and, it is believed, has not, in general, previously been successfully used, with full effectiveness, for psychopharmacologic or psychotropic agents. Transdermal delivery is accompanied by its own side effects, including a potential for skin irritation, arising from the gel or other matrix, from the pharmaceutical itself, or from the interaction of the pharmaceutical with the matrix. Furthermore, a transdermal system must be configured such that the combination of the matrix and the pharmaceutical does not react with or modify the pharmaceutical, or otherwise render it ineffective, such that the combination provides sufficient diffusion coefficients, such that the delivery system is not adversely affected by expected temperature variations during normal manufacture, transportation, storage and use, such that the gel or other matrix retain the desired viscosity, and such that the pharmaceutical can be properly dispersed or dissolved in the matrix such that components remain homogenous and do not separate (particularly when more than one pharmaceutical is included) and the like.

Although other forms of delivery of pharmaceuticals agents are known, each has its drawbacks. Parenteral (i.e., intravenously or intramuscularly injected) administration is inconvenient and expensive, and is rarely used outside the hospital. Inhalation is believed to be not feasible with psychopharmacologic agents currently in use or with many other pharmaceuticals.

Accordingly, it would be useful to provide a transdermal delivery system effective to provide good transdermal absorption and acceptable plasma blood levels preferably a system which can be adapted for use with a wide variety of different agents for transdermal delivery of effective amounts of such agents at a desired or controlled rate, while preferably avoiding or reducing undesired effects such as liver damage, gastrointestinal side effects, sedation, and weight gain.

SUMMARY OF THE INVENTION

The present invention provides for transdermal delivery of pharmacologic agents, particularly psychopharmacologic, anti-convulsant, anti-inflammatory, analgesic or other agents, by dissolving or dispersing such agents in a gel, preferably a lecithin organogel. In one embodiment, an agent is delivered using a lecithin gel such as a gel formed using lecithin and an organic solvent such as isopropyl palmitate or isopropyl myristate, alcohol, or ethoxy diglycol. In one embodiment, the gel includes or is formed from a polymer such as that sold under the trade name "Pluronic" available from BASF-Wyandotte Corporation, Parsippany, N.J.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 is a depiction of an evaluation form used in evaluating an embodiment of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

One class of psychopharmacologic agents, some of whose members can be administered according to embodiments of

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the present invention, are serotonin specific reuptake inhibitors (SSRIs). SSRIs are commonly prescribed for patients with diagnoses of mood disorders, some forms of anxiety disorder (particularly panic disorder), obsessive compulsive disorders, some forms of menopausal disorders, and eating disorders (especially bulimia nervosa). Examples of such SSRIs include sertraline (sold under the trade name Zoloft), paroxetine (sold under the trade name Paxil), fluoxetine (sold under the trade name Prozac), venlafaxine (sold under the trade name Effexor), and fluvoxamine (sold under the trade name Luvox). Although many patients tolerate oral administration of these SSRIs, a certain population of patients experience gastrointestinal side effects. Without wishing to be bound by any theory, it is believed that such side effects may be relatively frequent for SSRIs in part because the gastrointestinal system is richly endowed with serotonin receptors and that SSRIs may result in such side effects as alterations in gastric motility, nausea, and diarrhea. Medically healthy individuals may tolerate oral dosing with SSRIs with difficulty, or not at all. Medically compromised patients, for example patients with gastric or duodenal ulcer, ulcerative colitis, irritable colon syndrome or regional enteritis may not be able to tolerate the oral form of these medications and thus, in the absence of alternative administration routes, may be deprived of helpful antidepressant pharmacotherapeutic treatment.

Another class of psychopharmacologic agents which may be administered according to embodiments of the present invention include antidepressants such as bupropion (sold under the trade name Wellbutrin), reboxetine (sold under the trade name Edronax), nefazodone (sold under the trade name Serzone) and trazadone (sold under the trade name Desyrel). Although these antidepressant medications are often well tolerated by the gastrointestinal (GI) system, in some cases, oral preparations have resulted in malabsorption problems or idiosyncratic side effects, which, in some cases, may be avoided by transdermal administration according to embodiments of the present invention, as described more thoroughly below.

Yet another category of psychopharmacologic agents are mood stabilizing medications, examples of which include carbamazepine (sold under the trade name Tegretol) and valproic acid (sold under the trade name Depakote). These agents are used frequently in psychiatric practice as either augmentation medications (to render antidepressants more effective) or as anti-manic medications in the treatment of bipolar mood disorder. They are also used in neurologic practice for the treatment of seizure disorders and for the treatment of certain pain disorders. Many patients have difficulty tolerating the gastrointestinal side effects of these medications, most typically nausea. Such side effects are particularly troublesome for these agents since compliance with rigorously regular medication schedules is of great clinical importance to many of these patients. Accordingly, transdermal delivery according to embodiments of the present invention is particularly helpful in achieving compliance with a regular medication schedule.

Another type of psychopharmaceutical agent are those used for treating Attention Deficit Hyperactivity Disorder (ADHD), one example of which is pemoline, sold under the trade name Cylert. Pemoline is a medication that is used in

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the treatment of Attention Deficit Hyperactivity Disorder in children and adults. It is practically insoluble in water, but soluble in ethylene glycol and lipids, making it a good candidate for transdermal administration. Its principal problem in medical practice is its association with chemical hepatitis (hepatotoxicity). Since approximately 80% of orally ingested pemoline goes through the liver prior to reaching the bloodstream (called first pass metabolism), transdermal administration, which bypasses the liver, may offer a significant advantage in reducing liver metabolism. It is anticipated that the incidence of chemical hepatitis might be significantly lower for transdermally administered pemoline.

Another type of psychopharmaceutical agent includes dopamine agents, used for treating Parkinson's disease, examples of which are pergolide, sold under the trade name Permax and bromocriptine mesylate, sold under the trade name Parlodel. Oral administration of dopamine agents such as pergolide or bromocriptine mesylate may be sub-optimal because of GI irritation. Accordingly, transdermal delivery of dopamine agents such as pergolide and bromocriptine mesylate, according to embodiments of the present invention, is particularly useful.

Another type of psychopharmaceutical agent are those used for treating depression and/or neuropathic pain, two examples of which are generically available amitriptyline, sold under the trade name Elavil and doxepin sold under the tradename Sinequan. Oral administration of amitriptyline and doxepin may be sub-optimal when high local tissue concentrations are desired. Accordingly, transdermal delivery of amitriptyline and doxepin, according to embodiments of the present invention, is particularly useful.

In some situations, a transdermal composition containing a combination of doxepin or amitriptyline with carbamazepine or gabapentin is useful for treating neuropathic pain. It is believed that transdermal administration of such combination can be advantageous, for at least some patients, as compared to oral administration, because higher local drug concentrations at the site(s) e.g. of injury can be achieved yielding an improved therapeutic response without systemic side effects such as weight gain, drowsiness, gastrointestinal upset and anticholinergic side effects (which include but are not limited to urinary retention, blurred vision and dry mouth).

Another type of psychopharmaceutical agent are those used for treating hypertension and akathisia, one example of which is propranolol, sold under the trade name Inderal. Oral administration of propranolol may be sub-optimal because of rare GI intolerance or malabsorption. Accordingly, transdermal delivery of propranolol according to embodiments of the present invention is particularly useful.

Another class of pharmaceutical that may be particularly useful for localizing the dosage via transdermal applications are anticonvulsant agents such as generically available carbamazepine and patent protected gabapentin (sold respectively under the trade names Tegretol and Neurontin). Gabapentin is an anticonvulsant agent that is believed to relieve pain by blocking GABA-B neuroreceptor pain sites. Both gabapentin and carbamazepine often relieve muscle spasms, and therefore alleviate chronic pain through that mechanism as well. In oral form, gabapentin has been described as

useful for chronic pain and reflex sympathetic dystrophy. It has been found to be useful for alleviating the neuropathic component of pain resulting from cervical, thoracic, and lumbar spinal disk injury. Transdermal application of gabapentin and carbamazepine are particularly effective means of obtaining higher local tissue concentrations of the medications, avoiding many systemic side effects, which can include fatigue, lethargy, and dizziness. The combinations described in some of the examples below are means of adding to the antispasmodic and analgesic properties of the gabapentin and carbamazepine.

Another type of pharmaceutical that may be useful for transdermal application are those used for their analgesic and anti-inflammatory properties, or pain relief, such as ketoprofen and other non-steroidal anti-inflammatory drugs. For some patients, combinations of ketoprofen, doxepin, guaifenesin and/or carbamazepine have been demonstrated to be useful, e.g., for the treatment of superficial inflammation and swelling in combination with neuropathic pain, for example, in carpal tunnel syndrome, cervical disk and lumbar disk degenerative disease, occipital neuralgia, knee injuries including cartilage tears and joint surface damage, and similar degenerative processes involving the ankle and elbow. It has been demonstrated that administration of a combination of ketoprofen with other agents, particularly doxepin, gabapentin, and guaifenesin, can, for a majority of patients be useful as compared to oral agents, because it is believed that a composition combining ketoprofen with these agents provides substantially synergistic results, i.e. such that results are greater than the sum of results from ketoprofen alone in a transdermal application plus results from such additional components. It appears that the synergistic effect is most apparent when actual superficial swelling and inflammation is present; otherwise, use of the doxepin in combination with an anticonvulsant such as carbamazepine or gabapentin produces results that are not enhanced by the addition of ketoprofen. In some cases, guaifenesin has yielded a significant improvement in reduction of spasms, superior to that achieved with either carbamazepine or gabapentin. Guaifenesin is a centrally acting muscle relaxant. It is soluble in water, 1 gm at 25 degrees, and soluble in some organic solvents. Thus it appears to be on the border of oil and water solubility. Without wishing to be bound by any theory, it is believed this attribute may help explain, at least in part, the utility of guaifenesin (and, for similar reasons, fluoxetine) as a transdermal agent.

Another type of pharmaceutical that may be useful for transdermal administration includes pharmaceuticals used in treatment of impotence such as sildenafil, sold under the tradename Viagra. It is believed that transdermal administration of sildenafil may be useful, for at least some patients, as compared to oral administration which has been found, in at least some situations, to be associated with gastrointestinal side effects. Reports of deaths of sildenafil users may be an additional reason to consider a transdermal application method.

According to embodiments of the present invention, tablets, capsules or other preparations of psychopharmacologic agents or other pharmaceuticals, e.g., intended for oral delivery, were crushed and dispersed or dissolved in a gel formed of soya lecithin and isopropyl palmitate or isopropyl

myristate, alcohol, or ethoxy diglycol. In some cases, Pluronic gel, formed of Pluronic such as Pluronic F127, potassium sorbate and water was formed.

Without wishing to be bound by any theory, it is believed the degree to which pharmaceutical compounds will successfully diffuse or be transdermally transported through the skin into blood vessels is related in part to properties of lipid solubility. Lipid solubilities of pharmaceuticals are, to some extent, inversely proportional to their aqueous solubility, which is in part a function of the compound's polarity. Therefore, fluoxetine hydrochloride, which has limited aqueous solubility and apparent moderate lipid solubility, is transdermally transported whereas venlafaxine and bupropion, it is currently believed, are not transported particularly effectively. The oil-water coefficient is believed to be partially predictive of the degree to which a given compound, theoretically, can be transdermally transported. However, because the physical properties of these complex organic compounds are neither fully determined nor documented and because other factors may be significant, (any some of which are understood) it is not possible to predict, other than in approximate (general terms, their potential for (and thus the advisability of testing for) transdermal transport. These physical properties are particularly complex and difficult to forecast, e.g., because of the molecular mechanical release and retention properties of organogel lecithin, which contains a very long chain polymer (Pluronic) that has been demonstrated to vary widely, e.g., with temperature, percentage composition of the gel, and concentration of the pharmaceutical.

Detailed examples of the preparation are provided below, along with examples of results obtained or expected from transdermal administration to human patients. Typically, the gel preparation was or will be applied to either volar surface of the lower arm of the patient, the post-auricular (behind the ear) region, or at the painful site when treating neuropathic pain. Laboratory measures of plasma blood levels were or will be obtained as shown in the examples below. The results generally demonstrate or are expected to demonstrate good absorption transdermally using lecithin organogel matrix as the vehicle. In circumstances where the objective was to treat neuropathic or chronic pain, only local effects were required and plasma blood levels were not obtained. Some patients were or will be evaluated by means of a structured evaluation form (FIG. 1), completed at a frequency of at least one time per week. Patients were or will be evaluated both for all the present symptoms as well as any side effects from currently administered medications. This is believed to make it possible to note changes on an ongoing basis. In general, for psychiatric patients, those with the most clear cut and uncomplicated diagnoses of major depression experienced, or are expected to experience, the best results. Patients with severe personality disorders or with concealed substance abuse disorders generally did less well.

EXPERIMENTAL

EXAMPLE 1

One hundred grams of lecithin soya (granular) and 0.66 grams sorbic acid (NF-FCC powder) were dispersed in 100 grams (117 milliliters (mL)) of isopropyl palmitate NF and

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allowed to stand overnight. Approximately 220 milliliters of lecithin-isopropyl palmitate in a form of a liquid of a syrup consistency was formed.

EXAMPLE 2

One hundred grams of lecithin soya (granular) and 0.66 grams sorbic acid (NF-FCC powder) is dispersed in 100 grams (117 milliliters) of isopropyl myristate NF and allowed to stand overnight. Approximately 220 milliliters of lecithin-isopropyl myristate in a form of a liquid of a syrup consistency is formed.

EXAMPLE 3

A beaker was prepared by measuring to a volume of 100 milliliters. It was considered important to measure the volume accurately rather than using beaker markings. An amount of Pluronic F127 NF (20 grams for a 20 percent gel, 30 grams for a 30 percent gel, 40 grams for a 40 percent gel) was mixed with 0.3 grams potassium sorbate NF. Refrigerated purified water was added in an amount sufficient to bring the volume to 100 milliliters. When all of the granules had been wet the gel was refrigerated. Solution took place upon cooling, taking 12 to 24 hours. The resulting 100 milliliters of Pluronic gel was kept refrigerated, since the gel will solidify at room temperature.

EXAMPLE 4

Nine grams of carbamazepine in tablet form was ground in mortar and pestle. 4.3 milliliters of ethoxy diglycol was added and mixed to form a creamy paste. 13.2 milliliters of soya lecithin was added and mixed until smooth. The resulting 24 cc of solution was put into a 60 cc syringe. About 36 cc Pluronic F127 gel 20 percent (made according to Example 3) was placed in another syringe. The material was mixed well between syringes to yield 60 cc of carbamazepine organogel having a strength of 150 milligrams (mg) per milliliter. In some cases, the mixture was run through an ointment mill to reduce particle size.

EXAMPLE 5

Sixty 100 milligram tablets of bupropion were ground and strained to form a fine powder. The bupropion powder was dissolved in 30 cc purified water, placed in a filter and washed with 10 to 20 cc purified water. The filtrate was used to make a 20 percent Pluronic gel using the procedures from Example 3, substituting filtrate for an equivalent volume of water, and stored in a refrigerator. Thirteen milliliters of soya lecithin was mixed with one-half the bupropion Pluronic gel and mixed between syringes to form a first batch. Thirteen milliliters of soya lecithin was mixed with the second half of the bupropion Pluronic gel and mixed between syringes to form a second batch. To each batch was added sufficient Pluronic gel F127 (made according to example 3) to yield a total of two 60 cc batches of bupropion HCl organogel having a strength of 15 milligrams per milliliter.

EXAMPLE 6

600 milligrams of fluoxetine HCl (in the form of thirty 20 milligram capsules) was placed in a beaker and dissolved in

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approximately 18 cc of 95 percent ethyl alcohol. The solution was filtered through a filter funnel using fine filter paper. The residue was washed with 95 percent alcohol. The filtrate was heated, maintaining a temperature less than 85° C., to evaporate the alcohol to concentrate to 1 to 2 milliliters. 600 milligrams of isopropyl palmitate was combined with 600 milligrams of soya lecithin (granular), set aside and allowed to liquefy. Upon liquefaction, a thick syrupy consistency was obtained. 1.2 grams of the mixture was drawn into a 10 milliliter syringe and the alcoholic solution of fluoxetine HCl was drawn into another syringe. The two syringes were attached together with a Luer-Luer adapter and the gel was thoroughly mixed. All of the organogel was then transferred into one syringe and the empty syringe was disconnected. Sufficient quantity of 20 percent Pluronic F127 gel (formed as described in Example 3) was drawn into the empty syringe to make a total of 6 milliliters when added to the volume in the other syringe. A Luer-Luer adapter was attached and the contents of the two syringes was remixed until a smooth creamy mixture was obtained. All the mixture was transferred into one syringe, the empty syringe was removed and the Luer-Luer adapter was removed.

A Luer-oral adapter was attached to the mixture and transferred to six 1 milliliter oral syringes, was filled with 1 milliliter of the gel. In this way, each syringe contained five 20 milligram doses, or ten 10 milligram doses to yield a total of 60 doses of fluoxetine in lecithin organogel having a strength of 10 milligrams per 0.1 milliliters.

EXAMPLE 7

Twelve 250 milligram tablets of nefazadone were crushed in a mortar and pestle and put through a strainer. 4.8 milliliters of ethoxy diglycol (8 percent) was added and mixed. In cases in which all particles were not dissolved, 2 milliliters of Pluronic were added and mixed. 13.6 milliliters of soya lecithin were added and mixed. The resulting mixture was put into syringes with a Luer adapter and mixed well. Sufficient Pluronic F127 gel, prepared according to Example 3, was added to achieve a volume of 60 cc and mixed well to yield 60 cc of nefazadone organogel having a strength of 50 milligrams per milliliter.

EXAMPLE 8

Thirty 40 milligram tablets of paroxetine were crushed and run through a strainer, discarding green coating material. 4.8 milliliters of ethoxy diglycol was added to the powder and mixed in a mortar and pestle. Forty milliliters of Pluronic F127 gel 20 percent, formed according to Example 3, was added in graduated amounts to the powder and mixed until smooth using a spatula. 13.2 milliliters of soya lecithin was added and mixed well and the resulting material placed into syringes and sufficient quantity of Pluronic gel was added to bring the volume to 60 milliliters. In those such cases where particle size of the resulting material was too large, the cream was run through an ointment mill to yield 60 milliliters of paroxetine organogel having a strength of 20 milligrams per milliliter.

EXAMPLE 9

Thirty 100 milligram tablets of sertraline were crushed into a fine powder and strained, discarding the yellow

coating. Sufficient amount of Pluronic F127 gel 20 percent (formed according to Example 3) was added to achieve a volume of 38 milliliters and mixed well in a mortar and pestle until a smooth cream was achieved. This material was placed into syringes and mixed between the syringes to obtain a compact cream. 13.2 milliliters of soya lecithin was added and mixed well between the syringes using about 20 pumps. Sufficient quantity of Pluronic F127 gel 20 percent was added to yield 60 milliliters of sertraline gel having a strength of 15 milligrams per milliliter.

EXAMPLE 10

Venlafaxine hydrochloride has a solubility in water of 572 mg/mL (adjusted to ionic strength of 0.2 M with sodium chloride). Forty-five 100 milligram tablets of venlafaxine were crushed and put through a strainer. The powder was dissolved in 15 cc purified water, the solution placed into a filter and washed with 10 cc purified water. The filtrate was used to make a 20 percent Pluronic gel using the procedures of Example 3 (substituting the filtrate for an equivalent amount of water) and placed into a refrigerator overnight. 13.2 milliliters of soya lecithin were drawn into a syringe with a Luer loc. The venlafaxine Pluronic gel was drawn into another syringe coupled to the first syringe and mixed well. Sufficient Pluronic F127 gel was added to achieve a volume of 60 cc with a strength of 75 mg. per cc.

EXAMPLE 11

15 grams of sodium valproate (Depakote) was ground in mortar and pestle. 4 mL of ethoxy diglycol was added and mixed well to form a creamy paste. 19.8 mL of soya lecithin was added and mixed until smooth. The resulting 24 cc of solution was put into 2 syringes with a Luer Loc and mixed well. The mixture was divided so that half is in each syringe. Using another 60 cc syringe, Pluronic 30% gel was added to each to bring each syringe to a volume of 45 mL.

EXAMPLE 12

Paroxetine hydrochloride has a solubility in water of 5.4 mg/mL. Paroxetine (Paxil) gel was prepared, according to the procedures of example 8. A dosage of 40 mg per day was self-administered by a 59 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 210 days, blood was drawn and blood serum level of Paxil was determined to be 0 nanograms (ng) per mL, while typical reference levels are 49 ± 26 ng/mL, indicating possible poor absorption or lab error. Clinical evaluation of the patient over a 210 day period of such transdermal administration indicated benefit to patient without GI side effects similar to that noted with oral preparation.

EXAMPLE 13

Sertraline hydrochloride is slightly soluble in water and isopropyl alcohol and sparingly soluble in ethanol. Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 100 mg per day was self-administered by a 54 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 19 days, blood was drawn and blood

serum level of Zoloft was determined to be 5 ng/mL, while typical reference levels are 30–200 mg/mL indicating possible limited absorption or lab error.

EXAMPLE 14

Fluoxetine hydrochloride has a solubility in water of 14 mg/mL. Fluoxetine (Prozac) gel was prepared, according to the procedures of example 6. A dosage of 20 mg per day was self-administered by a 54 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7 days, blood was drawn and blood serum level of fluoxetine was determined to be 45 ng/mL, while the plasma level of the primary active metabolite norfluoxetine was also 45 ng/mL. There was evidence of patient benefit from the clinical evaluation.

EXAMPLE 15

Carbamazepine is practically insoluble in water and soluble in alcohol and in acetone. Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 400 mg per day was self-administered by a 55 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 120 days, blood was drawn and blood serum level of Tegretol was determined to be 4.6 micrograms (μ g) per mL, while typical therapeutic levels are 4–10 μ g/mL indicating good absorption. There were no GI side effects and the patient demonstrated clinical improvement.

EXAMPLE 16

Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 200 mg per day was self-administered by a 53 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 60 days, blood was drawn and blood serum level of Tegretol was determined to be 10.8 μ g/mL, while typical therapeutic levels are 4–10 μ g/mL indicating excellent absorption. There were no GI side effects and the patient demonstrated clinical improvement.

EXAMPLE 17

Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 50 mg per day was self-administered by a 53 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 63 days, blood was drawn and blood serum level of Zoloft was determined to be 23 ng/mL, while typical reference levels are 30–200 mg/mL. The patient demonstrated a good clinical response without GI side effects.

EXAMPLE 18

Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 200 mg per day was self-administered by a 47 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 91 days, blood was drawn and blood serum level of Tegretol was determined to be less than 0.5 μ g/mL, while typical therapeutic levels are 4–10 μ g/mL, indicating poor absorption, lab error, or patient non-compliance.

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EXAMPLE 19

Bupropion is highly soluble in water. Bupropion (Wellbutrin) gel was prepared, according to the procedures of example 5. A dosage of 100 mg per day was self-administered by a 47 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 44 days, blood was drawn and blood serum level of Wellbutrin was determined to be less than 0.5 ng/mL, while typical therapeutic levels are 10–30 indicating poor absorption, lab error, or patient non-compliance.

EXAMPLE 20

Fluoxetine gel was prepared, according to the procedures of example 6. Typically, a total daily adult dosage of fluoxetine as applied to the skin according to the present invention is between about 20 mg and 200 mg, more preferably between about 120 mg and about 200 mg. Dosages for non-adults and/or non-human mammals may need to be adjusted, e.g. proportionally to body weight. A dosage of 20–60 mg per day was self-administered by 5 patients, including that of example 13 and also including a 44 year old male patient, a 53 year old female patient, a 47 year old male patient and a 36 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 30–180 day period of such transdermal administration indicated a clinical response ranging from complete remission of symptoms to moderate improvement.

EXAMPLE 21

Fluoxetine gel was prepared, according to the procedures of example 6. A dosage of 80–160 mg per day was self-administered by a 50 year old female by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7 days at the 80 mg dosage level blood was drawn and the blood serum of fluoxetine was determined to be 34 ng/mL fluoxetine and 25 ng/mL norfluoxetine, while typical reference levels are 50–480 ng/mL, indicating good absorption. There was evidence of patient benefit from the clinical evaluation. The dosage was then increased to 160 mg per day and administered by the same method. After 7 days at the 160 mg dosage level blood was drawn and the blood serum level of fluoxetine was determined to be 90 ng/mL fluoxetine and 25 ng/mL norfluoxetine, indicating good absorption. There was evidence of increased patient benefit at this higher dosage level which correlated positively with the higher plasma level. The patient has been receiving the medication continuously for a period of 5 months.

EXAMPLE 22

Fluoxetine gel was prepared, according to the procedures of example 6. A dosage of 80–160 mg/day was self-administered by a 38 year old female by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7 days at the 80 mg dosage level, blood was drawn and the blood serum level of fluoxetine was determined to be 25 ng/mL of fluoxetine and 25 ng/mL norfluoxetine. There was evidence of patient benefit from the clinical evaluation. The

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dosage was then increased to 160 mg per day and administered by the same method.

EXAMPLE 23

Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 50–200 mg per day was self-administered by 6 patients, including those of examples 12 and 16 and also including a 60 year old male patient, a 53 year old male patient, a 48 year old male patient, a 38 year old male patient and a 47 year old male patient, by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 7–90 day period of such transdermal administration indicated responses ranging from complete resolution of depression to no noticeable response.

EXAMPLE 24

Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 200–400 mg per day was self-administered by 6 patients, including those of examples 14, 15 and 17, and also including a 48 year old female patient, a 48 year old male patient and a 54 year old female patient, by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. The clinical evaluation of the patients over a 30–300 day period of such transdermal administration indicated responses ranging from moderate improvement to no positive clinical response.

EXAMPLE 25

Paroxetine (Paxil) gel was prepared, according to the procedures of example 8. A dosage of 20 mg per day was self-administered by the patient of example 12 as well as by a 15 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. Clinical evaluation of the patients over a 30–210 day period of such transdermal administration indicated equivocal clinical improvement of the depression which may (or may not) have been related to the transdermally administered Paxil.

EXAMPLE 26

Five 150 mg tablets of amitriptyline were crushed and run through a strainer. The powder was put into syringes with a Luer Loc and mixed well with 2 mL ethoxy diglycol. About 6 mL Pluronic Gel 20% was added and mixed well. 6.6 mL Soya Lecithin was added and mixed well. This mixture was thinned to 30-mL, total volume with Pluronic Gel 20% and mixed well. The resulting mixture having a strength of 25 mg/mL was placed in appropriate dispensing device.

EXAMPLE 27

Amitriptyline (Elavil) gel was prepared, according to the procedure of example 26. A dosage of 25 mg per day was self-administered by a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 100 day period of such transdermal administration indicated an

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apparently good clinical response, comparable to that achieved with oral medication.

EXAMPLE 28

Trazodone (Desyrel) gel was prepared, according to a procedure similar to that of example 7. A dosage of 50–150 mg per day was self-administered by 2 patients, including a 36 year old female patient and a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 42–90 day period of such transdermal administration indicated a good to excellent clinical response.

EXAMPLE 29

Venlafaxine (Effexor) gel was prepared, according to a procedure similar to that of example 9. A dosage of 150–225 mg per day was self-administered by 2 patients, including a 54 year old female patient and a 55 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 15–165 day period of such transdermal administration indicated a response ranging from no clinical improvement to mild clinical improvement.

EXAMPLE 30

Propranolol (Inderal) gel was prepared, according to a procedure similar to that of example 8 to produce a gel having a strength of 40 mg of propranolol per mL of gel. A dosage of 80 mg per day was self-administered by 2 patients, including a 36 year old female patient and a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 100 day period of such transdermal administration indicated results comparable to those achieved with oral medication.

EXAMPLE 31

Bupropion (Wellbutrin) gel was prepared, according to a procedure described in example 5. A dosage of 150–200 mg, per day was self-administered by 3 patients, including that of example 18, and also including a 38 year old male patient and a 53 year old female patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 5–45 day period of such transdermal administration indicated equivocal results.

EXAMPLE 32

Valproic acid (Depakote) gel was prepared, according to a procedure similar to that of example 4. A dosage of 1000 mg per day was self-administered by a 38 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 30 day period of such transdermal administration indicated results comparable to those achieved with oral medication.

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EXAMPLE 33

Valproic acid (Depakote) gel was prepared according to the procedure of example 11. A dosage of 500–1000 mg was self administered by two male patients, ages 41 and 49. Administration was by application to the skin, for a period of at least one hour. Significant skin irritation occurred with one patient, but no gastrointestinal side effects were reported. Clinical evaluation of the patients over a period of two months revealed improvement, but upon longer term follow-up it appeared that other factors may have been responsible. After 28 days, blood was drawn and a serum valproic acid level of 26 $\mu\text{g/mL}$ was obtained for the 49 year old patient (while taking 250 mg twice daily), with a therapeutic reference range of 50–150 $\mu\text{g/mL}$. This indicated poor to fair absorption, and the dosage was raised to 500 mg twice daily, with a further improvement in clinical response. The 41 year old patient reported a good clinical response to an initial dosage of 250 mg administered twice daily, but a serum valproic acid level of only 1 $\mu\text{g/mL}$ was obtained. The dosage was increased to 500 mg twice daily, and a similar serum valproic acid level was obtained. The disparity between the clinical response and the plasma level might be explained either by laboratory error or placebo effect.

EXAMPLE 34

A gel containing reboxetine (sold under the trade name Edronax) is prepared according to a procedure similar to that described in example 5 but using reboxetine in place of bupropion. The resulting mixture will be self administered by patients by application to the skin for a period of at least 1 hour. No skin irritation or gastrointestinal side effects are expected. Clinical evaluation of patients over a 5–45 day period of such transdermal administration is expected to indicate a good response to treatment.

EXAMPLE 35

Nefazodone (Serzone) gel was prepared, according to a procedure described in example 7. A dosage of 100 mg per day was self-administered by a 61 year old (male, female) patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 21 day period of such transdermal administration indicated a good response to treatment.

EXAMPLE 36

1 gram of permoline tablets are crushed in a mortar and then dissolved in propylene glycol, just sufficient to effect dissolution. 3 mL of propylene glycol or 95% ethyl alcohol is added to form a paste. 6.6 mL soya lecithin is added to the mixture in the mortar. The mixture is placed in two syringes with a Luer Loc and mixed thoroughly. Each syringe is filled to 30 mL Pluronic F127 20% gel and mixed between syringes to produce a mixture having a strength of 33 mg/mL. The mixture is put in an appropriate dispensing device.

EXAMPLE 37

A 16-year-old female with an established diagnosis of Attention Deficit Disorder had been treated successfully

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with oral pemoline (Cylert) for about 6 months. To potentially decrease the risk of liver damage associated with long-term use, pemoline prepared according to the procedure of example 36 will be administered transdermally, by application to the skin in the post auricular region for a period of at least one hour, at two sites, twice daily. No skin irritation is expected. The clinical results are expected to be comparable to those obtained with the oral medication, although the dosage may have to be adjusted upwards to achieve adequate plasma levels, and more time may be required to achieve satisfactory plasma levels.

For psychiatric patients, some have received two or more psychopharmaceuticals, and in some cases, two or more of the above examples describe different evaluations for the same period of administration of a psychopharmaceutical agent.

Of the patients who have received prescriptions for one or more of the medications as described in the examples above, each had previously demonstrated a significant intolerance to oral administration of one or more medications, prior to instituting transdermal administration. The laboratory measures of plasma blood levels described above for transdermally administered fluoxetine and carbamazepine are believed to demonstrate good absorption transdermally using lecithin organogel matrix as the vehicle. Valproic acid and sertraline do not appear to be absorbed well or reliably. Valproic acid appears to cause skin irritation in some patients necessitating discontinuation. Both the laboratory measure of Bupropion and the patient clinical responses indicated poor or equivocal absorptions and results. Patient tolerance of transdermal administration has been good to excellent. Patients in the example above who suffered very severe GI side effects using oral preparations were more tolerant of the inconvenience of rubbing on the gel than were patients who had experienced only mild to moderate side effects. In general, more highly motivated and treatment-compliant patients also had a higher rate of sustained compliance.

Patients in the examples above were evaluated by means of a structured evaluation form depicted in FIG. 1, which was completed at a frequency of at least one time per week for each patient receiving transdermal medication according to the present invention. The patients were evaluated both for all present psychiatric symptoms as well as any side effects from currently-administered medications. In general, it is believed that patients with the most clear cut and uncomplicated diagnosis of major depression experienced the best results. In general, patients with severe personality disorders or with concealed substance abuse disorders did less well.

EXAMPLE 38

1800 mg of gabapentin in powder form is dissolved with 1 mL propylene glycol in syringes with a Luer Loc. 6.6 mL of Soya lecithin is added and mixed thoroughly between syringes. The resulting material is placed in a device for dispensing measured amounts.

EXAMPLE 39

Gabapentin mixtures of 2% and 4% will be prepared by substituting 1200 mg gabapentin or 600 mg gabapentin in place of 1800 mg gabapentin, in example 38.

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EXAMPLE 40

Gabapentin, prepared according to Example 38 or 39, will be combined with either 3% or 5% Lidocaine in varying ratios.

EXAMPLE 41

4% gabapentin, prepared according to Example 38 or 39, will be combined with 7% carbamazepine and 7% amitriptyline.

EXAMPLE 42

2% gabapentin, prepared according to Example 38 or 39, will be combined with 2% carbamazepine and 1% Piroxicam, which is expected to yield better penetration into muscle tissue.

EXAMPLE 43

Gabapentin, prepared according to Example 38 or 39, in concentrations ranging from 2%–6% will be combined with clonidine in concentrations between 0.2% and 0.3%.

EXAMPLE 44

A 56-year-old woman had painful upper and lower extremity spasms as a result of spastic quadriparesis resulting from an injury. Oral gabapentin, an anticonvulsant, had been administered previously, but had caused a "drugged" feeling, one of the commonly reported side effects with this agent. It was believed that use of transdermal gabapentin might provide local relief by achieving high local tissue concentrations near the site of administration without correspondingly elevated blood plasma levels. It is known that other anticonvulsants, such as carbamazepine, are useful in reducing neurogenic pain. Gabapentin's solubility in water exceeds 10%, making systemic absorption less likely. Gabapentin prepared according to the procedure of example 38 was self-administered by application to the skin in the area of pain. The patient reported moderate relief of spasms over a period of one week, with no systemic side effects and no report of skin irritation.

EXAMPLE 45

Six grams of amitriptyline powder was placed in 40 milliliters of Pluronic F127 33% gel and placed under refrigeration to dissolve. Two milliliters of ethoxy diglycol was added to 4.8 grams of carbamazepine and mixed to form a smooth paste. 16.4 grams of soya lecithin was added to the resulting paste and mixed well. The dissolved amitriptyline composition was added to the carbamazepine composition and sufficient Pluronic F127 20% was added to make 120 milliliters and the resulting composition was mixed well to yield a composition having 5% amitriptyline and 4% carbamazepine.

EXAMPLE 46

6 grams of doxepin was added to 20 milliliters Pluronic 33% F127 and put into a refrigerator to dissolve. 24 grams of ketoprofen and 12 grams of guaifenesin was added to 10 milliliters of 95% alcohol and mixed well. 26.4 milliliters of soya lecithin was added and mixed well and the doxepin

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composition was mixed with the ketoprofen/guaifenesin composition. The resulting mixture was added to sufficient Pluronic 33% to yield 120 milliliters. The resulting composition was mixed well to yield a composition having about 20% ketoprofen, 5% doxepin and 10% guaifenesin.

EXAMPLE 47

6 grams of doxepin was added to 26 milliliters Pluronic 33% and refrigerated to dissolve. 2 milliliters ethoxy diglycol was added 4.8 grams carbamazepine and mixed. The resultant mixture was added to 24 grams ketoprofen and six milliliters alcohol and the result was mixed well. 26.4 milliliters soya lecithin was added to the ketoprofen composition and mixed well. The doxepin composition was mixed with the carbamazepine/ketoprofen composition and sufficient Pluronic 33% was added to yield 120 milliliters. The resultant composition was mixed well to yield a composition having about 20% ketoprofen, 4% carbamazepine and 5% doxepin.

EXAMPLE 48

0.15 grams sildenafil was crushed and strained and dissolved in 5 milliliters Pluronic 20% F127 and mixed between syringes. 2.2 milliliters of soya lecithin was added and mixed. Sufficient Pluronic 20% was added to yield 10 milliliters and the resultant composition was mixed well to

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yield a composition having the strength of about 15 milligrams per milliliter.

EXAMPLE 49

A mixture of Sildenafil 15 mg/ml was applied to the penis and scrotum of a 51 year old male. An immediate and strong erection resulted with sexual stimulation, without any irritation or burning. It is believed the composition will possess the therapeutic results claimed for orally administered Sildenafil, without any time delay, without any systemic GI side effects, and possibly without the degree of drug interaction with nitrates used in cardiac disease. It is believed that this will contribute both to the convenience of use of the pharmaceutical and to its safety.

EXAMPLE 50

Compositions according the examples 45 through 47, 53, 55 were transdermally applied to numerous patients, for the purpose of treating pain including as described in other examples herein, with the results summarized in Table I below. The meaning of certain entries in Table I is indicated in Table II below. Blank results indicate no treatment at the pertinent site for this patient. Where a given line of Table I shows more than one site, one "best" (biggest pain relief) result if shown in bold.

TABLE 1

Patient	Age	Gender	Surgery	Pain	ketoprofen	gabapentin	piroxicam	Medication Wt. % in lecithin organogel				Duration	Shoulder	Back	Neck	Elbow	Knee	Wrist	Arm	Ankle	Hip	Leg
								doxepin	carbamazepine	amitriptyline	guaifenesin											
A	50	2	2	3	10	3	4	5				2		0								
B	61	1	1	3								4	2.0	2.0	2.0	2.0						
B	61	1	1	3				4				12		2.0	2.0							
B	61	1	1	3	10	4	3					6		1.0	2.0			3.0				
C	41	2	1	2				4		5		2										
D	53	1	2	1	10	4	1					1		2.0	.0							
E	57	2	2	3	10	4		5				1	1.0	2.0		1.5						1.0
E	57	2	2	3	10	4	3					2		2.0			1.0					
F	38	2	2	3				10			5	2				3.0						
F	38	2	2	3					4			2							1.5			
F	38	2	2	3	10	4	1		4			8	2.0						1.0			
G	39	1	1	2	20	4		5				4	2.0									
H	61	1	1	3	10	4	3		4			6		2.0		3.0						
I	49	1	1	3	10	4						4										
I	49	1	1	3				5			10	12						2.0				
I	49	1	1	3					4			1						1.0				
J	54	1	1	3				5		5		2		1.5				3.0				
K	40	1	1	3					5			2										
K	40	1	2	3	10		3	5				6	4.0									
L	55	2	2	3	10	4	3	6				4	1.0									
L	55	2	2	2				5				6	1.0						.0		1.5	2.0
M	38	1	2	1				4				2		3.0				.0				
N	47	2	1	2	20	2				5		3	1.5									
N	47	2	1	2	10	4	1					2	3.0	3.0	4.0		1.0					
O	57	2	1	2	20	4		5				24	.0		2.0			2.0				
O	57	2	2	2	10	4	3					24	2.0		3.0							
P	51	2	2	2	15	5		5				2	1.0	.0								
Q	51	2	1	2	20			5			10	2		4.0								
R	35	1	1	2					4	5		1		2.0			1.5					
R	35	1	1	2	10	4	1					0					.0					
S	55	1	1	2	10	4	1					1		1.0								
T	50	2	2	1	10	4						16				2.0	1.0			2.0		

TABLE 1-continued

Patient	Age	Gender	Surgery	Pain	ketoprofen	gabapentin	piroxicam	Medication Wt, % in lecithin organoel				Duration	Shoulder	Back	Neck	Elbow	Result (Best result in Bold)					Leg
								doxepin	carbamazepine	amitriptyline	guaifenesin						Knee	Wrist	Arm	Ankle	Hip	
U	45	1	2	2	10	4	3					2			.0							
V	57	2	1	3					6			8					3.0					
V	57	2	1	3	10	4	1					3					1.0					
W	35	1	2	1	10	4	1					8			1.0							
X	46	1	1	3	10			5	4			8			2.0	2.0						
Y	48	1	1	3	10			5				4			2.0							
Y	48	2	1	3	10	4	1					4				1.5	1.5				.0	
Z	53	1	1	3	10	4	3					12					1.0					
AA	53	2	2	1	10	4	1					4			1.0							
BB	58	2	1	3	20	4			4		1	8	hand	1.0							2.0	
CC	59	1	1	2				5				2		2.0	2.0		2.0			2.0		
CC	59	1	1	2	10	4	1					20		1.0	2.0		3.0	2.0		3.0		
CC	59	1	1	2	10	4	5					1					3.0					
DD	58	1	1	2	10	4	3					12			1.0							
EE	45	2	2	3	10	4	3					24	1.5		1.0							
FF	44	2	1	3	10	4	3					20	2.0		1.0							
GG	35	1	1	3	20	4						4					1.0					
GG	35	1	1	3				5				8						1.0				1.5
GG	35	1	1	3	20			5		5		2				1.0						
GG	35	1	1	3	20			5				2						2.0				
GG	35	1	1	3	20			5			10	2				1.0	2.5					
HH	40	1	2	2	10	4	3					4					1.0					
II	40	1	2	3								8										
II	40	1	1	3	10	4	3					8										
JJ	45	1	2	2	10	4	3					8										
KK	37	2	2	2	10	4	1					2										
LL	54	1	1	3	10	4	3					8										
LL	54	1	1	3								6					1.0					
MM	42	2	1	3		4			4	5		2										
MM	42	2	1	3	10	4	3					8			4.0			2.0				.0
MM	42	2	1	3								12			.0							
NN	41	1	2	2	10	4	3	5				4			.0			2.0		2.0		1.0

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TABLE II

Gender:	1 = male	2 = female	
Surgery:	1 = one or more surgeries	2 = no surgeries	
Pain:	1 = mild	2 = moderate	3 = severe-sufficient to produce observed tears
Duration: length of treatment trial in weeks			
Result:	0 = no benefit		
	1 = mild benefit		
	2 = moderate benefit (greater than 25% pain reduction)		
	3 = major benefit (greater than 40-45% pain reduction)		
	4 = almost complete relief (greater than 80% pain reduction)		

Certain results drawn from the information of Table I are summarized in Table III and IV.

TABLE III

Percent reported pain relief						
Site	N (Number of data points)	None	Mild	mild-moderate	moderate	major Total
Wrist	13	16.7	33.3	8.3	41.7	
Shoulder	14	7.1	21.4	14.3	42.9	7.1
Elbow	5		40	20	20	20
Back	25	24	32	8	28	8
Arm	7	28.6	14.3	14.3	28.6	14.3
Neck	11	9.1	18.2		45.5	9.1
Knee	13	15.4	46.2	15.4	7.7	15.4

TABLE IV

(percent reported pain relief)							
	N	None	Mild	mild-moderate	moderate	major	Total
Best result without tricyclic	36	16.7	36.1	8.3	27.8	8.3	2.8
Best result with any tricyclic	20	10	10	20	35	15	10
Either tricyclic-sole agent	7		14.3	14.3	42.9	14.3	14.3
Best result with ketoprofen gabapentin piroxicam	25	16	44	4	28	8	
Best result without doxepin	43	18.6	32.6	14	23.3	7	4.7
Best result with doxepin	13		7.7	7.7	53.8	23.1	7.7

EXAMPLE 51

A 51 year old female administered a composition prepared according to example 46, containing 20% ketoprofen, 5% doxepin, and 10% guaifenesin to her back for a period of 2 weeks. She reported moderate pain relief, lasting several hours, after each application. She reported no skin irritation nor any other side effects. Oral medications had produced no relief, and had caused significant GI side effects.

EXAMPLE 52

A 34 year old man administered a composition containing 20% ketoprofen, 4% carbamazepine, and 5% doxepin to a very severely scarred wrist that had undergone 4 surgeries for carpal tunnel syndrome. He reported moderate pain relief, lasting for several hours after each application. No

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other treatment, including opiate oral pain medication, had been effective in providing even minor pain relief.

EXAMPLE 53

24 grams ketoprofen and sufficient guaifenesin to result in a 10% final guaifenesin concentration, was mixed well with 10 milliliters 95% alcohol. 1200 mg gabapentin was dissolved in one ml propylene glycol in a syringe with a luer loc. 26.4 ml of soya lecithin was added to the ketoprofen-guaifenesin-alcohol mixture and mixed well. The resulting mixture was added to the gabapentin-propylene glycol mixture and mixed well. 4.8 gm of carbamazepine was combined with the resultant combination and mixed well to form a smooth paste. The resulting paste was combined with the ketoprofen-guaifenesin-alcohol-gabapentin mixture and mixed well with sufficient pluronic to yield 120 ml of a composition containing ketoprofen 20%, carbamazepine 4%, gabapentin 4%, guaifenesin 10%

EXAMPLE 54

58 year old female with damage to her cervical spinal cord with a resultant spastic quadraparesis reported moderate relief of both pain and muscle spasms when she applied a mixture prepared generally according to example 53, containing ketoprofen 20%, carbamazepine 4%, gabapentin 4%, guaifenesin 10% for a period of 8 weeks to her back and hip. She had been unable to tolerate both oral carbamazepine and oral gabapentin because of systemic side effects, including skin rash with the carbamazepine and dizziness and sedation

with the gabapentin. She experienced no skin irritation nor other side effects with the transdermal formulation.

EXAMPLE 55

Six grams of doxepin powder combined with 26 milliliters pluronic and placed in the refrigerator until dissolved. 1200 mg gabapentin was mixed with 1 ml propylene glycol and placed in a syringe with luer lock. 6.6 ml of soya lecithin was added and mixed well between syringes. 24 gm of ketoprofen and 8 milliliters alcohol was mixed well between two syringes with luer loc. The doxepin mixture was mixed well with the gabapentin mixture and subsequently the ketoprofen mixture was added and mixed well. Sufficient pluronic 20% (about 54 ml) was added to yield 60 ml of a composition having about 20% ketoprofen, 4% weight percent gabapentin and 5% weight percent doxepin.

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EXAMPLE 56

A 57 year old female applied a mixture, prepared generally according to example 55, containing ketoprofen 20%, gabapentin 4%, and doxepin 5% for a period of 8 weeks to her neck and reported major relief. She applied the same mixture to her shoulder and reported moderate relief. A mixture that substituted piroxicam for the doxepin produced only mild shoulder relief.

EXAMPLE 57

A 35 year old man with a history of knee injury with vascular compromise and 3 surgeries applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% amitriptyline to his knee, and reported mild to moderate pain relief, without skin irritation nor other side effects.

EXAMPLE 57A

A 41 year old woman with history of back surgery applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% gabapentin to her back for a period of 2 weeks. She reported mild pain relief.

EXAMPLE 58

A 53 year old man with a history of two total bilateral knee replacements applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% amitriptyline to both knees for a period of 4 weeks. He reported no pain relief.

EXAMPLE 58A

A 54 year old man with a history of 7 back surgeries applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% amitriptyline to his back for a period of 2 weeks. He reported mild to moderate pain relief, over and above that he was receiving from a transdermal opiate medication (Duragesic). He reported no side effects, and specifically no skin irritation.

EXAMPLE 59

A 38 year old man with a history of shoulder strain applied a mixture, prepared generally according to example 45, containing 4% carbamazepine and 5% amitriptyline to his shoulder for a period of 2 weeks. He reported mild to moderate pain relief, and reported no skin irritation nor other side effects.

EXAMPLE 61

Sufficient carbamazepine and gabapentin was added to a combination of soya lecithin and pluronic to yield a lecithin organogel having about 4% carbamazepine and 5% gabapentin.

EXAMPLE 62

A 42 year old woman with a history of 3 back surgeries and cervical degenerative disc disease applied a mixture, prepared according to example 61, containing 4% carbamazepine and 5% gabapentin to her neck and reported total relief of pain. She reported no side effects, and no skin

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irritation. She noted the complete and rapid resolution of a migraine like headache at the same time. Administration of the same mixture to her arm and her wrist, affected by a diagnosed condition of reflex sympathetic dystrophy, yielded moderate pain relief.

EXAMPLE 63

3.6 grams gabapentin was dissolved with 5.4 ml ethoxy diglycol using a mortar and pestle. 9.6 grams ketoprofen and 2.7 grams piroxicam were added and the resultant composition mixed well. 19.8 milliliters soya lecithin was added and resultant mixture mixed well and added to a sufficient quantity of 20% pluronic gel to yield 90 milliliters of a composition having about 10 percent ketoprofen, 4% gabapentin and 3% piroxicam.

EXAMPLE 64

3.6 grams gabapentin was dissolved with 5.4 ml ethoxy diglycol using a mortar and pestle. 9 grams ketoprofen and 0.9 grams piroxicam were added and mixed well. 19.8 milliliters soya lecithin was added to the resultant mixture and mixed well. Sufficient amount of pluronic gel 20% was added to yield 90 milliliters of a composition having approximately 10% ketoprofen, 4% gabapentin and 1% piroxicam.

EXAMPLE 65

12 g doxepin was mixed with 50 ml Pluronic F 127 33% and placed in a refrigerator to dissolve. 12 g gabapentin was dissolved in 9 ml ethoxy diglycol and mixed to form a smooth paste. 52.8 ml of soya lecithin was added and mixed well. The doxepin/Pluronic mixture was added and mixed well. Sufficient quantity of Pluronic F 127 20% was added to produce 240 ml of a composition having about 5 wt % gabapentin and 5 wt % doxepin.

EXAMPLE 66

A 36 year old man with a knee injury involving joint surface damage and vascular compromise applied a mixture, prepared generally according to Example 65 to his knee several times per day. He reported moderate to major (40%) relief of pain that persisted for 4 to 6 hours. An earlier trial of carbamazepine-amitriptyline gel produced no relief when applied to his knee.

EXAMPLE 67

6 gm doxepin was mixed with 18 ml of Pluronic 33% to and placed in a refrigerator to dissolve. 6 gm gabapentin was ground in a mortar and pestle to a fine powder, added to 6 ml ethoxy diglycol and mixed to form a smooth paste. 12 gm guaifenesin was added and mixed well. 26.4 ml soya lecithin was added and mixed well. The doxepin/Pluronic mixture was added and mixed well. Sufficient quantity of Pluronic gel (25.2 ml of 33% Pluronic, although 30% or 20% Pluronic can be used), was added to produce 120 ml of a composition having about 5 wt % gabapentin, about 5 wt % doxepin and about 10 wt % guaifenesin.

EXAMPLE 68

A 55 year old woman with a back and shoulder injury sustained as a nursing care provider applied a mixture,

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prepared generally according to Example 67, to her back three times per day for a period of two weeks and achieved major relief. She applied the same mixture to her hip and leg and reported moderate to major relief. A mixture containing only doxepin provided only moderate relief to her back, and mild to moderate relief to her hip and leg. A mixture that contained only ketoprofen, gabapentin and piroxicam provided only mild relief to her back.

EXAMPLE 69

A 59 year old woman with cervical and back strain applied a mixture, prepared generally according to example 51, but without steps involving ketoprofen) containing about 5 wt % doxepin and about 10 wt % guaifenesin, to her neck for a period of two weeks, two to four times per day, and achieved total relief. She applied the same mixture to her back and achieved major to total relief.

EXAMPLE 70

4.5 gm of doxepin HCl was dissolved using 2.5 ml 95% alcohol and mixed well between syringes. It is also possible to mix the doxepin with 5 ml Pluronic 20% and place in a refrigerator to dissolve. Sufficient quantity of 20% Pluronic F127 was added to produce 90 ml of a composition having about 5 wt % doxepin. Preferably this and other disclosed compositions are protected from light.

EXAMPLE 71

A 61 year old man with injuries to his back, neck and arm applied a mixture (prepared generally according to Example 70) to his neck four times per day and achieved major relief. He applied the same mixture to his elbow and achieved moderate relief.

Based at least partially on the results described herein, a number of conclusions can be drawn. It appears doxepin is an effective neuropathic pain medication when administered transdermally and appears to be substantially free of side effects when administered by means of the gel utilized as a transport vehicle as described herein. Doxepin appears to provide about three times the positive response rate compared to at least some other pharmaceutical agents described herein, regardless of whether such other pharmaceutical agents are administered singly or in combination. Doxepin appears to be substantially more effective than amitriptyline as a neuropathic pain agent when administered transdermally. This appears to be true regardless of whether doxepin is administered as a single agent or is administered in combination with other pharmaceuticals as described herein. Carbamazepine appears to provide positive effects as a neuropathic pain agent, at least in properly selected patients. Carbamazepine appears to cause a rash in at least some patients, requiring its discontinuation. These side effects appear similar to those that are noted for oral administration of carbamazepine. Gabapentin appears to be free of side effects when administered transdermally. Although some patients appear to derive some benefit from a combination of transdermally administered ketoprofen, gabapentin, and piroxicam, the effect appears to be relatively weak compared to the effect provided by doxepin. Guaifenesin appears to provide benefit at least as an adjunctive treatment, of painful

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spasticity. There are some difficulties in combining guaifenesin with doxepin in gel to yield a stable non-separating mixture. In many situations it appeared that a patient who applied an analgesic gel to more than one site described different degrees of pain relief for different body parts. For the patient population described herein, amitriptyline appeared to offer only limited pain relief when administered transdermally. It appears that combining gabapentin with doxepin may offer some additional benefit. The addition of guaifenesin to doxepin may be of particular value when painful spasticity is present.

In light of the above description, a number of advantages of the present invention can be seen. The present invention provides for psychopharmaceutical and other pharmaceutical treatment using a transdermal delivery system. The invention makes it possible to provide such treatment to patients for whom oral delivery is suboptimal, such as patients who experience gastrointestinal or other side effects, patients who experience poor absorption for orally delivered pharmaceuticals and/or patients who benefit from delivery over an extended period or a relatively rapid delivery or higher rate of increase of plasma levels. The present invention is able to achieve delivery of therapeutic amounts of pharmaceuticals, for at least some patient populations, substantially without skin irritation, gastrointestinal or other side effects associated with orally-delivered pharmaceuticals, especially psychopharmaceuticals, and yields clinical benefits comparable to or greater than those received by patients to whom corresponding pharmaceuticals were administered orally. Although numerous examples of compositions which appear to be useful are disclosed herein, it is currently believed that among the most effective neuropathic pain medications are those described in examples 65, 67, 69 and 70.

A number of variations and modifications of the invention can also be used. It is believed that blood plasma levels may be increased by providing for two or more transdermal applications per day and/or applying a transdermal composition to two or more sites. At least partially on the basis of results described herein it is believed at least some other tricyclic components in a lecithin organogel will prove to be useful. In addition to amitriptyline and doxepin, examples of other tricyclic and related components include imipramine, trimipramine, clomipramine, nortriptyline, protriptyline, desipramine, maprotiline, amoxapine and trazodone.

In at least one case, application of a Prozac gel formulation twice daily appeared to approximately double the plasma level. It is believed that an approach such as applying a Prozac gel formulation twice daily to two sites will yield middle range therapeutic levels of about 140–250 ng/ml. At least partially on the basis of the results described herein for fluoxetine, it is believed olanzapine (sold under the trade name Zyprexa) or a fluoxetine/olanzapine mixture in a lecithin organogel will prove useful.

Other types of psychotropic or psychopharmaceutical medications for which the described transdermal delivery may be used including psychostimulant medications. One example of a psychostimulant medication is Methylphenidate (sold under the trade name Ritalin) used in the treatment of attention deficit hyperactivity disorder (ADHD). Methylphenidate typically has a 2–4 hour duration of action

necessitating frequent dosing of a patient which is particularly difficult to accomplish with children in school. It is believed that by using transdermal administration, it will be possible to achieve an extension of effective dosing throughout the day, eliminating the need for frequent oral medication administration. It is believed that transdermal administration will also eliminate peaks and valleys of blood plasma levels which, it is believed, will be more clinically effective. It is believed similar results will be obtained with other pharmaceuticals, for example, Dextroamphetamine (under the trade name Dexedrine) although it is believed the need is less acute since a time release "spansule" form of the medication is available which typically has a 5-6 hour duration of action. Another group of psychotropic medications which, it is believed, will benefit from transdermal delivery includes antipsychotic medication such as those used in the treatment in schizophrenia.

Embodiments of the invention include, but are not necessarily limited to, use by patients with enteric absorption deficits.

Although, in at least some of the embodiments described above, the pharmaceutical was provided by crushing and/or sieving tablets which include fillers or binders in addition to the pharmaceutical, the present invention can also be used by mixing, with the gel, the pharmaceutical in a relatively pure form, without filler. It is believed that this approach is likely to improve pharmaceutical delivery. In some embodiments, selected enzymes or other materials that act as transdermal delivery enhancers may be included. Carriers such as organogel lecithin matrix may be enhanced or replaced by, for example, reverse micelles (water and oil microemulsions) and/or liposomes (lipid vesicles).

Although the present invention has been described by way of self-administered doses in the form of a gel applied to the skin by the patient, the present invention can also be implemented by providing the transdermal preparation in premeasured doses preferably in connection with an adhesive or other covering or patch so that the dosage may be administered e.g. by placing the adhesive patch on the skin of the patient. Although some embodiments of the invention have been described in connection with positioning the pharmaceutical gel on the arm of a patient, other positioning on the skin of a patient can also be used. Because, depending on the formulation, speed or duration of transdermal delivery may vary as function of skin location, in one embodiment the location of the skin to which the pharmaceutical is applied is selected so as to relatively increase or decrease the delay, speed, duration, or rate of delivery of the pharmaceutical, either with respect to a particular tissue or systemically. For example, when a rapid rise in blood serum levels is desired, a placement which enhances delivery rate, such as behind the ear, can be used. When it is desired to enhance dose or delivery rate locally, the transdermal formulation may be positioned adjacent the desired treatment area. Membranes or matrices, such as a polymer matrix, may be used to limit or control delivery rates. In addition to transdermal gel or patch delivery, delivery of the transdermal or aerosol formulation can be achieved, e.g. by administration as nosedrops, cardrops, eyedrops and/or suppositories.

Although lecithin organogel has been described as a delivery matrix, other lecithin materials can be used includ-

ing lecithin combined with Pluronic Gel, or Carbopol. Although the examples above describe a gel which combines lecithin organogel with a polymer gel such as Pluronic gel, lecithin gel can be provided without combining with Pluronic gel or may be combined with other gels such as Carbopol. Although in some of the above examples, pharmaceuticals were combined with gels to provide concentration such that an effective dose occupies between about 1 mL and about 2 mL, other ratios can be used to provide for larger or smaller volume of gel per effective dose. Although a lecithin or lecithin gel carrier is described, it is believed transdermal delivery of at least some of the prescribed pharmaceuticals can be achieved using other carriers, or without using any carrier. Unless otherwise noted, an effective dose refers to a mass or volume delivered across the skin. Preferably, an effective dose is delivered to the target tissue or systemically in an amount or manner to achieve therapeutically helpful amounts or concentrations in the target tissue or systemically (such as indicated by a blood plasma level).

In one embodiment, medications dispensed in transdermal gel form will be dispensed in unit doses, such as blister packs. The gel will be extruded from the blister pack, and rubbed on the administration site. The dosage will be adjusted by varying the number of unit dose applied. This will ensure accurate dosimetry and will avoid contamination of the gel.

Although the application has been described by way of a preferred embodiment and certain variations and modifications, other variations and modification can also be used, the invention being defined by the following claims.

What is claimed is:

1. A transdermal composition comprising a psychopharmaceutical and guaifenesin in an amount effective to treat pain, and lecithin organogel.

2. The composition of claim 1, wherein said psychopharmaceutical is selected from the group consisting of sertraline, fluoxetine, carbamazepine, amitriptyline, trazodone, fluvoxamine, pemoline, pergolide, bromocriptine mesylate, propranolol, bupropion, reboxetine, valproic acid, nefazodone and doxepin.

3. The composition of claim 1, wherein said psychopharmaceutical is doxepin.

4. A transdermal composition comprising doxepin and guaifenesin in an amount effective to treat pain, and lecithin organogel.

5. The composition of any of claims 4, further comprising Pluronic F127.

6. A transdermal composition comprising doxepin guaifenesin in an amount effective to treat pain, Pluronic F127, and lecithin organogel.

7. The composition of any one of claims 1, 4, or 6, comprising about 5 wt % doxepin.

8. The composition of any one of claims 1, 4, or 6, comprising about 10 wt % guaifenesin.

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9. The composition of any one of claims 1, 4, or 6, comprising about 5 wt % doxepin and about 10 wt % guaifenesin.

10. A transdermal composition suitable for treating pain comprising about 5 wt % doxepin, about 10 wt %⁵ guaifenesin, and lecithin organogel.

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11. A transdermal composition suitable for treating pain comprising about 5 wt % doxepin, about 10 wt % guaifenesin, Pluronic F127, and lecithin organogel.

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(54) Title: METHOD AND COMPOSITION FOR TRANSDERMAL ADMINISTRATION OF PHARMACOLOGIC AGENTS

(57) Abstract

A method and composition for transdermal delivery of psychopharmaceuticals is provided. The psychopharmaceuticals are delivered using a matrix of a lecithin gel such as a lecithin organogel. A number of psychopharmaceuticals can be used including fluoxetine, bupropion, reboxetine, carbamazepine, valproic acid, sertraline, fluvoxamine, nefazodone, trazadone, amitriptylene, propranolol, permoline, pergolide and bromocriptine mesylate. An evaluation form is depicted in the Figure.

Patient: _____ Date: _____	
Current Medications:	1) _____ 2) _____ 3) _____ 4) _____ 5) _____ 6) _____
Diagnosis:	Axis 1: _____ Axis 2: _____ Axis 3: _____ Axis 4: _____
Subjective: _____ _____ _____ _____ _____	
Objective:	APPEARANCE _____ AFFECT _____ SPEECH _____ CONCENTRATION _____ MEMORY _____ IRRITABILITY _____ APPETITE _____ ANXIETY _____ CRYING SPELLS _____ ENERGY LEVEL _____ SLEEP _____ WEIGHT _____
SIDE EFFECTS: _____	
RESPONSE OF DEPRESSION SYMPTOMS TO MEDICATIONS: EXCELLENT GOOD FAIR POOR NA	
RESPONSE OF ANXIETY SYMPTOMS TO MEDICATIONS: EXCELLENT GOOD FAIR POOR NA	
CONCURRENT MEDICATION CONDITIONS: _____	
ASSESSMENT: _____ _____ _____ _____	
PLAN: 1) Continue meds: _____ 2) Change dosage: _____ 3) New Med: _____ 4) _____	
LAB STUDIES ORDERED: _____ OTHER: _____	

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METHOD AND COMPOSITION FOR TRANSDERMAL ADMINISTRATION OF PHARMACOLOGIC AGENTS

The present invention is directed to transdermal administration of pharmacologic agents, especially psychopharmacologic agents and in particular to transdermal administration of drugs including serotonin specific reuptake inhibitors (as SSRIs) such as fluoxetine, antidepressants such as bupropion and reboxetine, mood stabilizers such as carbamazepine, or valproic acid, Attention Deficit Hyperactivity Disorder (ADHD) medications such as pemoline and or anti-convulsants such as gabapentin, such as using a gel matrix, preferably a lecithin organogel and/or a polymer gel.

BACKGROUND INFORMATION

Recently, and particularly over the last fifteen years or so, patients suffering from a wide variety of conditions have been successfully treated by administration of psychopharmacologic or psychotropic agents. A vast majority of such patients receive doses of these agents orally. Unfortunately, in some situations, oral administration of such psychopharmacologic agents has been infeasible or ineffective. In some cases, oral administration is associated with side effects, particularly gastrointestinal side effects, which cannot be tolerated well by the patient. In other cases, malabsorption of oral preparation have resulted in subtherapeutic plasma levels. In other cases, the psychopharmacologic agents have relatively short plasma half-lives, necessitating inconveniently frequent dosing. In general, oral delivery involves a time delay as the pharmaceutical is absorbed via the digestive system before entering the bloodstream. A number of psychopharmacologic agents which have traditionally been administered orally or by injection have been inappropriate or suboptimal for some patients when so-administered. In some cases, dosages which are appropriate for oral administration, upon being distributed more or less uniformly throughout the body, are undesirably low in a particular tissue to achieve desired results. Oral or injection administration of psychopharmacologic agents may result in too slow or too rapid increase in blood plasma levels, e.g. may involve an undesirably long time delay as the pharmaceutical is absorbed by the digestive system before entering the bloodstream, or may result in a "spike" in blood plasma levels followed by an undesirably low level, where a more

constant level would be preferable. Some pharmaceuticals are particularly prone to cause or contribute to liver damage when administered orally.

One alternative route of administration for selected pharmaceuticals, has been transdermal delivery. Transdermal delivery has been utilized, e.g., for the treatment of high blood pressure, for ischemic heart disease and for hormone replacement. Transdermal delivery is not necessarily appropriate for all types of pharmaceuticals and, it is believed, has not, in general, previously been successfully used, with full effectiveness, for psychopharmacologic or psychotropic agents. Transdermal delivery is accompanied by its own side effects, including a potential for skin irritation, arising from the gel or other matrix, from the pharmaceutical itself, or from the interaction of the pharmaceutical with the matrix. Furthermore, a transdermal system must be configured such that the combination of the matrix and the pharmaceutical does not react with or modify the pharmaceutical, or otherwise render it ineffective, such that the combination provides sufficient diffusion coefficients, such that the delivery system is not adversely affected by expected temperature variations during normal use, such that the gel or other matrix retain the desired viscosity, and such that the pharmaceutical can be properly dispersed or dissolved in the matrix and the like.

Although other forms of delivery of psychopharmacologic and other pharmaceuticals agents are known, each has its drawbacks. Parenteral (i.e., intravenously or intramuscularly injected) administration is inconvenient and expensive, and is rarely used outside the hospital. Inhalation is believed to be not feasible with psychopharmacologic agents currently in use or with many other pharmaceuticals.

Accordingly, it would be useful to provide a transdermal delivery system effective to provide good transdermal absorption and acceptable plasma blood levels of psychotropic or psychopharmacologic agents, preferably a system which can be adapted for use with a wide variety of different psychopharmacologic agents for transdermal delivery of effective amounts of such agents at a desired or controlled rate, while preferably avoiding or reducing undesired effects such as liver damage.

SUMMARY OF THE INVENTION

The present invention provides for transdermal delivery of pharmacologic agents, particularly psychopharmacologic agents, by dissolving or dispersing such

agents in a gel, preferably a lecithin organogel. In one embodiment, an SSRI agent such as fluoxetine is delivered using a lecithin gel such as a gel formed using lecithin and an organic solvent such as isopropyl palmitate or isopropyl myristate. In one embodiment, the gel includes or is formed from a polymer such as that sold under the trade name "Pluronic" available from BASF-Wyandotte Corporation, Parsippany, New Jersey.

BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 is a depiction of an evaluation form used in evaluating an embodiment of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

One class of psychopharmacologic agents, some of whose members can be administered according to embodiments of the present invention, are serotonin specific reuptake inhibitors (SSRIs). SSRIs are commonly prescribed for patients with diagnoses of mood disorders, some forms of anxiety disorder (particularly panic disorder), obsessive compulsive disorders, some forms of menopausal disorders, and eating disorders (especially bulimia nervosa). Examples of such SSRIs include sertraline (sold under the trade name Zoloft), paroxetine (sold under the trade name Paxil), fluoxetine (sold under the trade name Prozac), venlafaxine (sold under the trade name Effexor), and fluvoxamine (sold under the trade name Luvox). Although many patients tolerate oral administration of these SSRIs, a certain population of patients experience gastrointestinal side effects. Without wishing to be bound by any theory, it is believed that such side effects may be relatively frequent for SSRIs in part because the gastrointestinal system is richly endowed with serotonin receptors and that SSRIs may result in such side effects as alterations in gastric motility, nausea, and diarrhea. Medically healthy individuals may tolerate oral dosing with SSRIs with difficulty, or not at all. Medically compromised patients, for example patients with gastric or duodenal ulcer, ulcerative colitis, irritable colon syndrome or regional enteritis may not be able to tolerate the oral form of these medications and thus, in the absence of alternative administration routes, may be deprived of helpful antidepressant pharmacotherapeutic treatment.

Another class of psychopharmacologic agents which may be administered according to embodiments of the present invention include antidepressants such as bupropion (sold under the trade name Wellbutrin), reboxetine (sold under the trade name Tegretol), nefazodone (sold under the trade name Serzone) and trazadone (sold under the trade name Desyrel). Although these antidepressant medications are often well tolerated by the gastrointestinal (GI) system, in some cases, oral preparations have resulted in malabsorption problems or idiosyncratic side effects, which, in some cases, may be avoided by transdermal administration according to embodiments of the present invention, as described more thoroughly below.

Yet another category of psychopharmacologic agents are mood stabilizing medications, examples of which include carbamazepine (sold under the trade name Tegretol) and valproic acid (sold under the trade name Depakote). These agents are used frequently in psychiatric practice as either augmentation medications (to render antidepressants more effective) or as anti-manic medications in the treatment of bipolar mood disorder. Many patients have difficulty tolerating the gastrointestinal side effects of these medications, most typically nausea. Such side effects are particularly troublesome for these agents since compliance with rigorously regular medication schedules is of great clinical importance to many of these patients. Accordingly, transdermal delivery according to embodiments of the present invention is particularly helpful in achieving compliance with a regular medication schedule.

Another type of psychopharmaceutical agent are those used for treating Attention Deficit Hyperactivity Disorder (ADHD), one example of which is pemoline, sold under the trade name Cylert. Pemoline is a medication that is used in the treatment of Attention Deficit Hyperactivity Disorder in children and adults. It is practically insoluble in water, but soluble in ethylene glycol and lipids, making it a good candidate for transdermal administration. Its principal problem in medical practice is its association with chemical hepatitis (hepatotoxicity). Since approximately 80% of orally ingested pemoline goes through the liver prior to reaching the bloodstream (called first pass metabolism), transdermal administration, which bypasses the liver, may offer a significant advantage in reducing liver metabolism. It is anticipated that the incidence of chemical hepatitis might be significantly lower for transdermally administered pemoline.

Another type of psychopharmaceutical agent includes dopamine agents, used for treating Parkinson's disease, examples of which are pergolide, sold under the trade name Permax and bromocriptine mesylate, sold under the trade name Parlodel. Oral administration of dopamine agents such as pergolide or bromocriptine mesylate may be sub-optimal because of GI irritation. Accordingly, transdermal delivery of dopamine agents such as pergolide and bromocriptine mesylate, according to embodiments of the present invention, is particularly useful.

Another type of psychopharmaceutical agent are those used for treating depression and/or chronic pain, one example of which is amitriptylene, sold under the trade name Elavil. Oral administration of amitriptylene may be sub-optimal when high local tissue concentrations are desired. Accordingly, transdermal delivery of amitriptylene, according to embodiments of the present invention, is particularly useful.

Another type of psychopharmaceutical agent are those used for treating hypertension and akathisia, one example of which is propranolol, sold under the trade name Inderol. Oral administration of propranolol may be sub-optimal because of rare GI intolerance or malabsorption. Accordingly, transdermal delivery of propranolol according to embodiments of the present invention is particularly useful.

Another type of pharmaceutical that may be particularly useful for localizing the dosage via transdermal applications are anticonvulsant/antispasmodic agents such as gabapentin (sold under the trade name Neurontin, an anticonvulsant medication that may also act as an antispasmodic agent. With relief of spasms, some pain relief is often experienced. In oral form, gabapentin is finding particular application in patients who have some neurologic component to cervical, thoracic, or low back pain. Transdermal application of gabapentin is expected to be a particularly effective means of obtaining higher local concentrations of the medication. The combinations described in some of the examples below are means of adding to the antispasmodic and analgesic properties of the gabapentin.

According to embodiments of the present invention, tablets, capsules or other preparations of psychopharmacologic agents or other pharmaceuticals, e.g., intended for oral delivery, were crushed and dispersed or dissolved in a gel formed of soya lecithin and isopropyl palmitate or isopropyl myristate. In some cases, Pluronic gel, formed of Pluronic such as Pluronic F127, potassium sorbate and water was formed.

Without wishing to be bound by any theory, it is believed the degree to which pharmaceutical compounds will successfully diffuse or be transdermally transported through the skin into blood vessels is related in part to properties of lipid solubility. Lipid solubilities of pharmaceuticals are, to some extent, inversely proportional to their aqueous solubility, which is in part a function of the compound's polarity. Therefore, fluoxetine hydrochloride, which has limited aqueous solubility and apparent moderate lipid solubility, is transdermally transported whereas venlafaxine and bupropion, it is currently believed, are not transported particularly effectively. The oil-water coefficient is believed to be partially predictive of the degree to which a given compound, theoretically, can be transdermally transported. However, because the physical properties of these complex organic compounds are neither fully determined nor documented and because other factors may be significant, (any some of which are understood) it is not possible to predict, other than in approximate general terms, their potential for (and thus the advisability of testing for) transdermal transport. These physical properties are particularly complex and difficult to forecast, e.g., because of the molecular mechanical release and retention properties of organogel lecithin, which contains a very long chain polymer (Pluronic) that has been demonstrated to vary widely, e.g., with temperature, percentage composition of the gel, and concentration of the pharmaceutical.

Detailed examples of the preparation are provided below, along with examples of results obtained or expected from transdermal administration to human patients. Typically, the gel preparation was or will be applied to the upper arm of the patient covering a surface of approximately 20 square centimeters. Laboratory measures of plasma blood levels were or will be obtained as shown in the examples below. The results generally demonstrate or are expected to demonstrate good absorption transdermally using lecithin organogel matrix as the vehicle. Some patients were or will be evaluated by means of a structured evaluation form (Fig. 1), completed at a frequency of at least one time per week. Patients were or will be evaluated both for all the present symptoms as well as any side effects from currently administered medications. This is believed to make it possible to note changes on an ongoing basis. In general, for psychiatric patients, those with the most clear cut and uncomplicated diagnoses of major depression experienced, or are expected to experience, the best

results. Patients with severe personality disorders or with concealed substance abuse disorders generally did less well.

Experimental

Example 1

5 One hundred grams of lecithin soya (granular) and 0.66 grams sorbic acid (NF-FCC powder) were dispersed in 100 grams (117 milliliters (mL)) of isopropyl palmitate NF and allowed to stand overnight. Approximately 220 milliliters of lecithin-isopropyl palmitate in a form of a liquid of a syrup consistency was formed.

Example 2

10 One hundred grams of lecithin soya (granular) and 0.66 grams sorbic acid (NF-FCC powder) is dispersed in 100 grams (117 milliliters) of isopropyl myristate NF and allowed to stand overnight. Approximately 220 milliliters of lecithin-isopropyl myristate in a form of a liquid of a syrup consistency is formed.

Example 3

15 A beaker was prepared by measuring to a volume of 100 milliliters. It was considered important to measure the volume accurately rather than using beaker markings. An amount of Pluronic F127 NF (20 grams for a 20 percent gel, 30 grams for a 30 percent gel, 40 grams for a 40 percent gel) was mixed with 0.3 grams potassium sorbate NF. Refrigerated purified water was added in an amount sufficient
20 to bring the volume to 100 milliliters. When all of the granules had been wet the gel was refrigerated. Solution took place upon cooling, taking 12 to 24 hours. The resulting 100 milliliters of Pluronic gel was kept refrigerated, since the gel will solidify at room temperature.

Example 4

25 Nine grams of carbamazepine in tablet form was ground in mortar and pestle. 4.3 milliliters of ethoxy diglycol was added and mixed to form a creamy paste. 13.2 milliliters of soya lecithin was added and mixed until smooth. The resulting 24 cc of solution was put into a 60 cc syringe. About 36 cc Pluronic F127 gel 20 percent

(made according to Example 3) was placed in another syringe. The material was mixed well between syringes to yield 60 cc of carbamazepine organogel having a strength of 150 milligrams (mg) per milliliter. In some cases, the mixture was run through an ointment mill to reduce particle size.

5 Example 5

Sixty 100 milligram tablets of bupropion were ground and strained to form a fine powder. The bupropion powder was dissolved in 30 cc purified water, placed in a filter and washed with 10 to 20 cc purified water. The filtrate was used to make a 20 percent Pluronic gel using the procedures from Example 3, substituting filtrate for an equivalent volume of water, and stored in a refrigerator. Thirteen milliliters of soya lecithin was mixed with one-half the bupropion Pluronic gel and mixed between syringes to form a first batch. Thirteen milliliters of soya lecithin was mixed with the second half of the bupropion Pluronic gel and mixed between syringes to form a second batch. To each batch was added sufficient Pluronic gel F127 (made according to example 3) to yield a total of two 60 cc batches of bupropion HCl organogel having a strength of 15 milligrams per milliliter.

Example 6

600 milligrams of fluoxetine HCl (in the form of thirty 20 milligram capsules) was placed in a beaker and dissolved in approximately 18 cc of 95 percent ethyl alcohol. The solution was filtered through a filter funnel using fine filter paper. The residue was washed with 95 percent alcohol. The filtrate was heated, maintaining a temperature less than 85° C, to evaporate the alcohol to concentrate to 1 to 2 milliliters. 600 milligrams of isopropyl palmitate was combined with 600 milligrams of soya lecithin (granular), set aside and allowed to liquefy. Upon liquefaction, a thick syrupy consistency was obtained. 1.2 grams of the mixture was drawn into a 10 milliliter syringe and the alcoholic solution of fluoxetine HCl was drawn into another syringe. The two syringes were attached together with a Luer-Luer adapter and the gel was thoroughly mixed. All of the organogel was then transferred into one syringe and the empty syringe was disconnected. Sufficient quantity of 20 percent Pluronic F127 gel (formed as described in Example 3) was drawn into the empty syringe to

make a total of 6 milliliters when added to the volume in the other syringe. A Luer-Luer adapter was attached and the contents of the two syringes was remixed until a smooth creamy mixture was obtained. All the mixture was transferred into one syringe, the empty syringe was removed and the Luer-Luer adapter was removed.

5 A Luer-oral adapter was attached to the mixture and transferred to six 1 milliliter oral syringes, was filled with 1 milliliter of the gel. In this way, each syringe contained five 20 milligram doses, or ten 10 milligram doses to yield a total of 60 doses of fluoxetine in lecithin organogel having a strength of 10 milligrams per 0.1 milliliters.

10 Example 7

Twelve 250 milligram tablets of nefazadone were crushed in a mortar and pestle and put through a strainer. 4.8 milliliters of ethoxy diglycol (8 percent) was added and mixed. In cases in which all particles were not dissolved, 2 milliliters of Pluronic were added and mixed. 13.6 milliliters of soya lecithin were added and
15 mixed. The resulting mixture was put into syringes with a Luer adapter and mixed well. Sufficient Pluronic F127 gel, prepared according to Example 3, was added to achieve a volume of 60 cc and mixed well to yield 60 cc of nefazadone organogel having a strength of 50 milligrams per milliliter.

Example 8

20 Thirty 40 milligram tablets of paroxetine were crushed and run through a strainer, discarding green coating material. 4.8 milliliters of ethoxy diglycol was added to the powder and mixed in a mortar and pestle. Forty milliliters of Pluronic F127 gel 20 percent, formed according to Example 3, was added in graduated amounts to the powder and mixed until smooth using a spatula. 13.2 milliliters of soya lecithin was
25 added and mixed well and the resulting material placed into syringes and sufficient quantity of Pluronic gel was added to bring the volume to 60 milliliters. In those such cases where particle size of the resulting material was too large, the cream was run through an ointment mill to yield 60 milliliters of paroxetine organogel having a strength of 20 milligrams per milliliter.

Example 9

Thirty 100 milligram tablets of sertraline were crushed into a fine powder and strained, discarding the yellow coating. Sufficient amount of Pluronic F127 gel 20 percent (formed according to Example 3) was added to achieve a volume of 38 milliliters and mixed well in a mortar and pestle until a smooth cream was achieved. This material was placed into syringes and mixed between the syringes to obtain a compact cream. 13.2 milliliters of soya lecithin was added and mixed well between the syringes using about 20 pumps. Sufficient quantity of Pluronic F127 gel 20 percent was added to yield 60 milliliters of sertraline gel having a strength of 15 milligrams per milliliter.

Example 10

Venlafaxine hydrochloride has a solubility in water of 572 mg/mL (adjusted to ionic strength of 0.2 M with sodium chloride). Forty-five 100 milligram tablets of venlafaxine were crushed and put through a strainer. The powder was dissolved in 15 cc purified water, the solution placed into a filter and washed with 10 cc purified water. The filtrate was used to make a 20 percent Pluronic gel using the procedures of Example 3 (substituting the filtrate for an equivalent amount of water) and placed into a refrigerator overnight. 13.2 milliliters of soya lecithin were drawn into a syringe with a Luer loc. The venlafaxine Pluronic gel was drawn into another syringe coupled to the first syringe and mixed well. Sufficient Pluronic F127 gel was added to achieve a volume of 60 cc with a strength of 75 mg. per cc.

Example 11

15 grams of sodium valproate (Depakote) was ground in mortar and pestle. 4 mL of ethoxy diglycol was added and mixed well to form a creamy paste. 19.8 mL of soya lecithin was added and mixed until smooth. The resulting 24 cc of solution was put into 2 syringes with a Luer Loc and mixed well. The mixture was divided so that half is in each syringe. Using another 60 cc syringe, Pluronic 30% gel was added to each to bring each syringe to a volume of 45 mL.

Example 12

Paroxetine hydrochloride has a solubility in water of 5.4 mg/mL. Paroxetine (Paxil) gel was prepared, according to the procedures of example 8. A dosage of 40 mg per day was self-administered by a 59 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 210 days, blood was drawn and blood serum level of Paxil was determined to be 0 nanograms (ng) per mL, while typical reference levels are 49 ± 26 ng/mL, indicating possible poor absorption or lab error. Clinical evaluation of the patient over a 210 day period of such transdermal administration indicated benefit to patient without GI side effects similar to that noted with oral preparation.

Example 13

Sertraline hydrochloride is slightly soluble in water and isopropyl alcohol and sparingly soluble in ethanol. Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 100 mg per day was self-administered by a 54 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 19 days, blood was drawn and blood serum level of Zoloft was determined to be 5 ng/mL, while typical reference levels are 30-200 mg/mL indicating possible limited absorption or lab error.

Example 14

Fluoxetine hydrochloride has a solubility in water of 14 mg/mL. Fluoxetine (Prozac) gel was prepared, according to the procedures of example 6. A dosage of 20 mg per day was self-administered by a 54 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7 days, blood was drawn and blood serum level of Prozac was determined to be 45/45 ng/mL, while typical reference levels are 50-480 ng/mL indicating good absorption. There was evidence of patient benefit from the clinical evaluation.

Example 15

Carbamazepine is practically insoluble in water and soluble in alcohol and in acetone. Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 400 mg per day was self-administered by a 55 year old male

patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 120 days, blood was drawn and blood serum level of Tegretol was determined to be 4.6 micrograms (μg) per mL, while typical therapeutic levels are 4-10 $\mu\text{g/mL}$ indicating good absorption. There were no GI side effects and the patient demonstrated clinical improvement.

Example 16

Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 200 mg per day was self-administered by a 53 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 60 days, blood was drawn and blood serum level of Tegretol was determined to be 10.8 $\mu\text{g/mL}$, while typical therapeutic levels are 4-10 $\mu\text{g/mL}$ indicating excellent absorption. There were no GI side effects and the patient demonstrated clinical improvement.

Example 17

Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 50 mg per day was self-administered by a 53 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 63 days, blood was drawn and blood serum level of Zoloft was determined to be 23 ng/mL, while typical reference levels are 30-200 mg/mL. The patient demonstrated a good clinical response without GI side effects.

Example 18

Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 200 mg per day was self-administered by a 47 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 91 days, blood was drawn and blood serum level of Tegretol was determined to be less than 0.5 $\mu\text{g/mL}$, while typical therapeutic levels are 4-10 $\mu\text{g/mL}$, indicating poor absorption, lab error, or patient non-compliance.

Example 19

Bupropion is highly soluble in water. Bupropion (Wellbutrin) gel was prepared, according to the procedures of example 5. A dosage of 100 mg per day was self-administered by a 47 year old male patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 44 days, blood was drawn and blood serum level of Wellbutrin was determined to be less than 0.5 ng/mL, while typical therapeutic levels are 10-30 indicating poor absorption, lab error, or patient non-compliance.

Example 20

Fluoxetine gel was prepared, according to the procedures of example 6.. Typically, a total daily adult dosage of fluoxetine as applied to the skin according to the present invention is between about 20mg and 200 mg, more preferably between about 20 mg and about 160 mg, more preferably about 80 mg. Dosages for non-adults and/or non-human mammals may need to be adjusted, e.g. proportionally to body weight. A dosage of 20-60 mg per day was self-administered by 5 patients, including that of example 13 and also including a 44 year old male patient, a 53 year old female patient, a 47 year old male patient and a 36 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 30-180 day period of such transdermal administration indicated a clinical response ranging from complete remission of symptoms to moderate improvement.

Example 21

Fluoxetine gel was prepared, according to the procedures of example 6. A dosage of 80-160 mg per day was self administered by a 50 year old female by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7 days at the 80 mg dosage level blood was drawn and the blood serum of fluoxetine was determined to be 34 ng/mL fluoxetine and 25 ng/mL norfluoxetine, while typical reference levels are 50-480 ng/mL, indicating good absorption. There was evidence of patient benefit from the clinical evaluation. The dosage was then increased to 160 mg per day and administered by the same method. After 7 days at the

160 mg dosage level blood was drawn and the blood serum level of fluoxetine was determined to be 90 ng/mL fluoxetine and 25 ng/mL norfluoxetine, indicating good absorption. There was evidence of increased patient benefit at this higher dosage level which correlated positively with the higher plasma level. The patient has been
5 receiving the medication continuously for a period of 5 months.

Example 22

Fluoxetine gel was prepared, according to the procedures of example 6. A dosage of 80-160 mg/day was self administered by a 38 year old female by application to the skin, for a period of at least 1 hour. No skin irritation was reported. After 7
10 days at the 80 mg dosage level, blood was drawn and the blood serum level of fluoxetine was determined to be 25 ng/mL of fluoxetine and 25 ng/mL norfluoxetine. There was evidence of patient benefit from the clinical evaluation. The dosage was then increased to 160 mg per day and administered by the same method.

Example 23

15 Sertraline (Zoloft) gel was prepared, according to the procedures of example 9. A dosage of 50-200 mg per day was self-administered by 6 patients, including those of examples 12 and 16 and also including a 60 year old male patient, a 53 year old male patient, a 48 year old male patient, a 38 year old male patient and a 47 year old male
20 patient, by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 7-90 day period of such transdermal administration indicated responses ranging from complete resolution of depression to no noticeable response.

Example 24

25 Carbamazepine (Tegretol) gel was prepared, according to the procedures of example 4. A dosage of 200-400 mg per day was self-administered by 6 patients, including those of examples 14, 15 and 17, and also including a 48 year old female patient, a 48 year old male patient and a 54 year old female patient, by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. The clinical evaluation of the patients over a 30-300 day period

of such transdermal administration indicated responses ranging from moderate improvement to no positive clinical response.

Example 25

Paroxetine (Paxil) gel was prepared, according to the procedures of example 8. A dosage of 20 mg per day was self-administered by the patient of example 12 as well as by a 15 year old female patient by application to the skin, for a period of at least 1 hour. No skin irritation was reported. Clinical evaluation of the patients over a 30-210 day period of such transdermal administration indicated moderate clinical improvement of depression.

Example 26

Five 150 mg tablets of amitriptylene were crushed and run through a strainer. The powder was put into syringes with a Luer Loc and mixed well with 2 mL ethoxy diglycol. About 6 mL Pluronic Gel 20% was added and mixed well. 6.6 mL Soya Lecithin was added and mixed well. This mixture was thinned to 30-mL total volume with Pluronic Gel 20% and mixed well. The resulting mixture having a strength of 25 mg/mL was placed in appropriate dispensing device.

Example 27

Amitriptyline (Elavil) gel was prepared, according to the procedure of example 23. A dosage of 25 mg per day was self-administered by a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 100 day period of such transdermal administration indicated an apparently good clinical response, comparable to that achieved with oral medication.

Example 28

Trazadone (Desyrel) gel was prepared, according to a procedure similar to that of example 7. A dosage of 50-150 mg per day was self-administered by 2 patients, including a 36 year old female patient and a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or

gastrointestinal side effects were reported. Clinical evaluation of the patients over a 42-90 day period of such transdermal administration indicated a good to excellent clinical response.

Example 29

5 Venlafaxine (Effexor) gel was prepared, according to a procedure similar to that of example 9. A dosage of 150-225 mg per day was self-administered by 2 patients, including a 54 year old female patient and a 55 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the
10 patients over a 15-165 day period of such transdermal administration indicated a response ranging from no clinical improvement to mild clinical improvement.

Example 30

Propranolol (Inderol) gel was prepared, according to a procedure similar to that of example 8 to produce a gel having a strength of 40 mg of propranolol per mL of gel.
15 A dosage of 80 mg per day was self-administered by 2 patients, including a 36 year old female patient and a 47 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 100 day period of such transdermal administration indicated results comparable to those achieved with oral
20 medication.

Example 31

Bupropion (Wellbutrin) gel was prepared, according to a procedure described in example 5. A dosage of 150-200 mg per day was self-administered by 3 patients, including that of example 18, and also including a 38 year old male patient and a 53
25 year old female patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 5-45 day period of such transdermal administration indicated equivocal results.

Example 32

Valproic acid (Depakote) gel was prepared, according to a procedure similar to that of example 4. A dosage of 1000 mg per day was self-administered by a 38 year old male patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 30 day period of such transdermal administration indicated results comparable to those achieved with oral medication.

Example 33

Valproic acid (Depakote) gel was prepared according to the procedure of example 11. A dosage of 500-1000 mg was self administered by two male patients, ages 41 and 49. Administration was by application to the skin, for a period of at least one hour. Minimal skin irritation and no gastrointestinal side effects were reported. Clinical evaluation of the patients over a period of two months indicated a good response to treatment. After 28 days, blood was drawn and a serum valproic acid level of 26 $\mu\text{g/mL}$ was obtained for the 49 year old patient (while taking 250 mg twice daily), with a therapeutic reference range of 50-150 $\mu\text{g/mL}$. This indicated fair absorption, and the dosage was raised to 500 mg twice daily, with a further improvement in clinical response. The 41 year old patient reported a good clinical response to an initial dosage of 250 mg administered twice daily, but a serum valproic acid level of only 1 $\mu\text{g/mL}$ was obtained. The dosage was increased to 500 mg twice daily, and a similar serum valproic acid level was obtained. The disparity between the clinical response and the plasma level might be explained either by laboratory error or placebo effect.

Example 34

A gel containing reboxetine (sold under the trade name Edronax) is prepared according to a procedure similar to that described in example 5 but using reboxetine in place of bupropion. The resulting mixture will be self administered by patients by application to the skin for a period of at least 1 hour. No skin irritation or gastrointestinal side effects are expected. Clinical evaluation of patients over a 5-45

day period of such transdermal administration is expected to indicate a good response to treatment.

Example 35

5 Nefazodone (Serzone) gel was prepared, according to a procedure described in example 7. A dosage of 100 mg per day was self-administered by a 61 year old (male, female) patient. Administration was by application to the skin, for a period of at least 1 hour. No skin irritation or gastrointestinal side effects were reported. Clinical evaluation of the patients over a 21 day period of such transdermal administration indicated a good response to treatment.

10 Example 36

1 gram of permoline tablets are crushed in a mortar and then dissolved in propylene glycol, just sufficient to effect dissolution. 3 mL of propylene glycol or 95% ethyl alcohol is added to form a paste. 6.6 mL soya lecithin is added to the mixture in the mortar. The mixture is placed in two syringes with a Luer Loc and mixed
15 thoroughly. Each syringe is filled to 30 mL Pluronic F127 20% gel and mixed between syringes to produce a mixture having a strength of 33 mg/mL. The mixture is put in an appropriate dispensing device.

Example 37

A 16-year-old female with an established diagnosis of Attention Deficit
20 Disorder had been treated successfully with oral permoline (Cylert) for about 6 months. To potentially decrease the risk of liver damage associated with long-term use, permoline prepared according to the procedure of example 36 will be administered transdermally, by application to the skin for a period of at least one hour. No skin irritation is expected. The clinical results are expected to be comparable to those
25 obtained with the oral medication, although the dosage may have to be adjusted upwards to achieve adequate plasma levels.

For psychiatric patients, some have received two or more psychopharmaceuticals, and in some cases, two or more of the above examples

describe different evaluations for the same period of administration of a psychopharmaceutical agent.

Of the patients who have received prescriptions for one or more of the medications as described in the examples above, each had previously demonstrated a significant intolerance to oral administration of one or more medications, prior to instituting transdermal administration. The laboratory measures of plasma blood levels described above for transdermally administered Fluoxetine, Valproic acid, Sertraline and Carbamazepine are believed to demonstrate good absorption transdermally using lecithin organogel matrix as the vehicle. The single laboratory measure of Paroxetine plasma level indicated poor absorption, laboratory error, or patient non-compliance. However, the patients' clinical response indicated positive medication effect. Both the laboratory measure of Bupropion and the patient clinical responses indicated poor or equivocal absorptions and results. Patient tolerance of transdermal administration has been good to excellent. Patients in the example above who suffered very severe GI side effects using oral preparations were more tolerant of the inconvenience of rubbing on the gel than were patients who had experienced only mild to moderate side effects. In general, more highly motivated and treatment-compliant patients also had a higher rate of sustained compliance.

Patients in the examples above were evaluated by means of a structured evaluation form depicted in Fig. 1, which was completed at a frequency of at least one time per week for each patient receiving transdermal medication according to the present invention. The patients were evaluated both for all present psychiatric symptoms as well as any side effects from currently-administered medications. In general, it is believed that patients with the most clear cut and uncomplicated diagnosis of major depression experienced the best results. In general, patients with severe personality disorders or with concealed substance abuse disorders did less well.

Example 38

1800 mg of gabapentin in powder form is dissolved with 1 mL propylene glycol in syringes with a Luer Loc. 6.6 mL of Soya lecithin is added and mixed thoroughly between syringes. The resulting material is placed in a device for dispensing measured amounts.

Example 39

Gabapentin mixtures of 2% and 4% will be prepared by substituting 1200 mg gabapentin or 600 mg gabapentin in place of 1800 mg gabapentin, in example 38.

Example 40

- 5 Gabapentin, prepared according to Example 38 or 39, will be combined with either 3% or 5% Lidocaine in varying ratios.

Example 41

4% gabapentin, prepared according to Example 38 or 39, will be combined with 7% carbamazepine and 7% amitriptylene.

10 **Example 42**

2% gabapentin, prepared according to Example 38 or 39, will be combined with 2% carbamazepine and 1% Piroxicam, which is expected to yield better penetration into muscle tissue.

Example 43

- 15 Gabapentin, prepared according to Example 38 or 39, in concentrations ranging from 2%-6% will be combined with clonidine in concentrations between .2% and .3%.

Example 44

- 20 A 56-year-old woman had painful upper and lower extremity spasms as a result of spastic quadriparesis resulting from an injury. Oral gabapentin, an anticonvulsant, had been administered previously, but had caused a "drugged" feeling, one of the commonly reported side effects with this agent. It was believed that use of transdermal gabapentin might provide local relief by achieving high local tissue concentrations near the site of administration without correspondingly elevated blood plasma levels. It is
25 known that other anticonvulsants, such as carbamazepine, are useful in reducing neurogenic pain. Gabapentin's solubility in water exceeds 10%, making systemic absorption less likely. Gabapentin prepared according to the procedure of example 38

was self-administered by application to the skin in the area of pain. The patient reported moderate relief of spasms over a period of one week, with no systemic side effects and no report of skin irritation.

In light of the above description, a number of advantages of the present invention can be seen. The present invention provides for psychopharmaceutical and other pharmaceutical treatment using a transdermal delivery system. The invention makes it possible to provide such treatment to patients for whom oral delivery is suboptimal, such as patients who experience gastrointestinal or other side effects, patients who experience poor absorption for orally delivered pharmaceuticals and/or patients who benefit from delivery over an extended period or a relatively rapid delivery or higher rate of increase of plasma levels. The present invention is able to achieve delivery of therapeutic amounts of pharmaceuticals, for at least some patient populations, substantially without skin irritation, gastrointestinal or other side effects associated with orally-delivered pharmaceuticals, especially psychopharmaceuticals, and have received clinical benefits comparable to or greater than those received by patients to whom corresponding pharmaceuticals were administered orally.

A number of variations and modifications of the invention can also be used. Other types of psychotropic or psychopharmaceutical medications for which the described transdermal delivery may be used including psychostimulant medications. One example of a psychostimulant medication is Methylphenidate (sold under the trade name Ritalin) used in the treatment of attention deficit hyperactivity disorder (ADHD). Methylphenidate typically has a 2-4 hour duration of action necessitating frequent dosing of a patient which is particularly difficult to accomplish with children in school. It is believed that by using transdermal administration, it will be possible to achieve an extension of effective dosing throughout the day, eliminating the need for frequent oral medication administration. It is believed that transdermal administration will also eliminate peaks and valleys of blood plasma levels which, it is believed, will be more clinically effective. It is believed similar results will be obtained with other pharmaceuticals, for example, Dextroamphetamine (under the trade name Dexedrine) although it is believed the need is less acute since a time release "spansule" form of the medication is available which typically has a 5-6 hour duration of action. Another group of psychotropic medications which, it is believed, will benefit from transdermal

delivery includes antipsychotic medication such as those used in the treatment in schizophrenia.

Embodiments of the invention include, but are not necessarily limited to, use by patients with enteric absorption deficits.

5 Although, in at least some of the embodiments described above, the pharmaceutical was provided by crushing and/or sieving tablets which include fillers or binders in addition to the pharmaceutical, the present invention can also be used by mixing, with the gel, the pharmaceutical in a relatively pure form, without filler. It is believed that this approach is likely to improve pharmaceutical delivery. In some
10 embodiments, selected enzymes or other materials that act as transdermal delivery enhancers may be included. Carriers such as organogel lecithin matrix may be enhanced or replaced by, for example, reverse micelles (water and oil microemulsions) and/or liposomes (lipid vesicles).

 Although the present invention has been described by way of self-administered
15 doses in the form of a gel applied to the skin by the patient, the present invention can also be implemented by providing the transdermal preparation in premeasured doses preferably in connection with an adhesive or other covering or patch so that the dosage may be administered e.g. by placing the adhesive patch on the skin of the patient. Although the invention has been described in connection with positioning the
20 psychopharmaceutical gel on the arm of a patient, other positioning on the skin of a patient can also be used. Because, depending on the formulation, speed or duration of transdermal delivery may vary as function of skin location, in one embodiment the location of the skin to which the pharmaceutical is applied is selected so as to relatively increase or decrease the delay speed duration, or rate of delivery of the pharmaceutical,
25 either with respect to a particular tissue or systemically. For example, when a rapid rise in blood serum levels is desired, a placement which enhances delivery rate, such as behind the ear, can be used. When it is desired to enhance dose or delivery rate locally, the transdermal formulation may be positioned adjacent the desired treatment area. Membranes or matrices, such as a polymer matrix, may be used to limit or
30 control delivery rates. In addition to transdermal gel or patch delivery, delivery of the transdermal or aerosol formulation can be achieved, e.g. by administration as nosedrops, eardrops, eyedrops and/or suppositories.

Although lecithin organogel has been described as a delivery matrix, other lecithin materials can be used including lecithin combined with Pluronic Gel, or Carbopol. Although the examples above describe a gel which combines lecithin organogel with a polymer gel such as Pluronic gel, lecithin gel can be provided without combining with Pluronic gel or may be combined with other gels such as Carbopol. Although in the above examples, pharmaceuticals were combined with gels to provide concentration such that an effective dose occupies between about 1 mL and about 2 mL, other ratios can be used to provide for larger or smaller volume of gel per effective dose. Although a lecithin or lecithin gel carrier is described, it is believed transdermal delivery of at least some of the prescribed pharmaceuticals can be achieved using other carriers, or without using any carrier. Unless otherwise noted, an effective dose refers to a mass or volume of fluoxetine delivered across the skin. Preferably, an effective dose is delivered to the target tissue or systemically in an amount or manner to achieve therapeutically helpful amounts or concentrations in the target tissue or systemically (such as indicated by a blood plasma level).

In one embodiment, medications dispensed in transdermal gel form will be dispensed in unit doses, such as blister packs. The gel will be extruded from the blister pack, and rubbed on the administration site. The dosage will be adjusted by varying the number of unit dose applied. This will ensure accurate dosimetry and will avoid contamination of the gel.

Although the application has been described by way of a preferred embodiment and certain variations and modifications, other variations and modification can also be used, the invention being defined by the following claims.

WHAT IS CLAIMED IS:

1. A composition comprising:
an effective amount of a psychopharmaceutical composition;
lecithin organogel;
- 5 2. The composition of claim 1, wherein said psychopharmaceutical is selected from the group consisting of sertraline, fluoxetine, carbamazepine, amitriptylene, trazadone, fluvoxamine, pemoline, pergolide, bromocriptine mesylate, propanolol, bupropion, reboxetine, valproic acid, and nefazodone.
- 10 3. A method for preparing a composition for transdermal delivery of a psychopharmaceutical comprising:
preparing a first psychopharmaceutical in liquid or finely-divided form;
mixing said psychopharmaceutical with lecithin organogel;
- 15 4. A method for treatment of humans comprising:
preparing a composition comprising a psychopharmaceutical and lecithin organogel;
applying to the skin of said human a volume of said composition containing an effective dose of said psychopharmaceutical.
- 20 5. A composition comprising carbamazepine and lecithin in a ratio of approximately 9 mg carbamazepine to 13.2 mL lecithin.
6. A composition comprising bupropion and lecithin in a ratio of about 6 g bupropion to 13.2 mL lecithin.
7. A composition comprising reboxetine and lecithin in a ratio of about 1 g reboxetine to 6.6 mL lecithin.
- 25 8. A composition comprising fluoxetine and lecithin in a ratio of about 600 mg fluoxetine dissolved in 95% ethyl alcohol reduced to 1-2 mL, combined with 1.4 mL lecithin.
9. A composition comprising nefazodone and lecithin in a ratio of about 3 g nefazodone to 13.6 mL lecithin.
- 30 10. A composition comprising pemoline and lecithin in a ratio of about 1.125 g pemoline to 6.6 mL lecithin.
11. A composition comprising sertraline and lecithin in a ratio of about 4.5 g sertraline to 13.2 mL lecithin.

12. A composition comprising pergolide and lecithin in a ratio of about 1 g pergolide to 6.6 mL lecithin.

13. A composition comprising bromocriptine mesylate and lecithin in a ratio of about 1 g bromocriptine mesylate to 6.6 mL lecithin.

5 14. A composition comprising fluvoxamine and lecithin in a ratio of about 1 g fluvoxamine to 6.6 mL lecithin.

15. A composition comprising amitriptylene and lecithin in a ratio of about 750 mg amitriptylene to 6.6 mL lecithin.

10 16. A composition comprising propranolol and lecithin in a ratio of about 1 g propranolol to 6.6 mL lecithin.

17. A composition comprising trazadone and lecithin in a ratio of about 1 g trazadone to 6.6 mL lecithin.

18. A composition comprising valproic acid and lecithin in a ratio of about 15 g sodium valproate to 19.8 mL lecithin.

15 19. A composition comprising about 600 mg fluoxetine, 600 mg isopropyl palmitate, 600 mg granular soya lecithin, 18 cc 95% ethyl alcohol and 6 milliliters 20% Pluronic gel.

20 20. A composition, as claimed in any of claims 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18, further comprising a sufficient quantity of 20% Pluronic F127 to provide a total volume of at least about 60 cc.

21. A method for treatment of mammals comprising:
preparing a composition comprising a pharmaceutical in finely-divided or liquid form, wherein said pharmaceutical is selected from the group consisting of

25 fluoxetine,
bupropion,
reboxetine,
carbamazepine,
valproic acid,
sertraline,
30 fluvoxamine,
nefazodone,
trazadone,
amitriptylene,

propanolol,
 permoline,
 pergolide,
 gabapentin, and
 5 bromocriptine mesylate;

applying to a first region the skin of said mammal a volume of said composition containing an effective dose of said pharmaceutical wherein said effective dose is delivered transdermally.

22. A method, as claimed in claim 1, wherein said method is used for
 10 treatment of humans.

23. A method, as claimed in claim 1, wherein said composition further comprises lecithin.

24. A method, as claimed in claim 1, wherein said composition further comprises lecithin organogel.

15 25. A method, as claimed in claim 1, wherein said composition comprises fluoxetine and lecithin in a ratio of about 600 mg fluoxetine to about 1.4 mL lecithin.

26. A method, as claimed in claim 1, wherein said composition further comprises a transdermal transport enhancer.

20 27. A method, as claimed in claim 1, further comprising selecting said first region for application of said composition so as to enhance the rate of increase in plasma level of fluoxetine.

28. A method for treatment of humans comprising:

dissolving fluoxetine in a liquid solvent;

25 mixing said dissolved fluoxetine with lecithin, Pluronic gel and a transdermal transport enhancer to form a therapeutic gel wherein the weight of fluoxetine per volume of lecithin is about 600 mg fluoxetine to 1.4 mL lecithin;

selecting a region of the skin of said human so as to increase the rate of increase in plasma level of fluoxetine, compared to at least one other area of the skin of said human, in response to application of said therapeutic gel to said region; and

30 applying said therapeutic gel to said region of the skin of said human.

29. A composition comprising fluoxetine and a gel in a ratio of about 600 mg fluoxetine per 1.4 mL gel, said gel selected to permit transdermal delivery of an effective dose of fluoxetine in response to application to the skin of a human.

30. A composition comprising:
 about 600 mg fluoxetine,
 about 600 mg isopropyl palmitate,
 about 600 mg granular soya lecithin,
 about 18 cc 95% ethyl alcohol; and
 about 6 milliliters 20% Pluronic gel.

31. A composition consisting essentially of:
 about 600 mg fluoxetine,
 about 600 mg isopropyl palmitate,
 about 600 mg granular soya lecithin,
 about 18 cc 95% ethyl alcohol; and
 about 6 milliliters 20% Pluronic gel.

32. A system for transdermal delivery of a pharmaceutical, comprising:
 a pharmaceutical selected from the group consisting of:

fluoxetine,
 bupropion,
 reboxetine,
 carbamazepine,
 valproic acid,
 sertraline,
 fluvoxamine,
 nefazodone,
 trazadone,
 amitriptylene,
 propanolol,
 permoline,
 pergolide,
 gabapentin, and
 bromocriptine mesylate; and

means for providing transdermal delivery of said pharmaceutical when
 applied to human skin.

33. A system, as claimed in claim 32, wherein said means for providing
 transdermal delivery comprises lecithin.

34. A system, as claimed in claim 32, wherein said means for providing transdermal delivery comprises an organogel.

35. A system, as claimed in claim 32, wherein said means for providing transdermal delivery comprises an adhesive patch.

5 36. A product for transdermal delivery of a pharmaceutical made by a process which comprises mixing a pharmaceutical selected from the group consisting of

fluoxetine,

bupropion,

10 reboxetine,

carbamazepine,

valproic acid,

sertraline,

fluvoxamine,

15 nefazodone,

trazadone,

amitriptylene,

propanolol,

permoline,

20 pergolide,

gabapentin, and

bromocriptine mesylate;

with lecithin to form a therapeutic mixture.

Patient: _____ Date _____

Current Medication: 1) _____
 2) _____
 3) _____
 4) _____
 5) _____
 6) _____

Diagnoses: Axis 1: _____ Axis 3: _____
 Axis 2: _____ GAF _____

Subjective: _____

Objective: APPEARANCE _____	AFFECT _____
SPEECH _____	CONCENTRATION _____
MEMORY _____	IRRITABILITY _____
APPETITE _____	AV HALLUC. _____
CRYING SPELLS _____	ENERGY LEVEL _____
SLEEP _____	WEIGHT _____

SIDE EFFECTS: _____

RESPONSE OF DEPRESSION SYMPTOMS TO MEDICATIONS:				
EXCELLENT	GOOD	FAIR	POOR	N/A
RESPONSE OF ANXIETY SYMPTOMS TO MEDICATIONS:				
EXCELLENT	GOOD	FAIR	POOR	N/A


CONCURRENT MEDICATION CONDITIONS: _____

ASSESSMENT: _____

PLAN: 1) Continue meds: _____
 2) Change dosage: _____
 3) New Med: _____
 4) _____

LAB STUDIES ORDERED: _____
 OTHER: _____

FIG. 1

A. CLASSIFICATION OF SUBJECT MATTER IPC(6) : A61F 13/02 US CL : 424/448 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 424/448		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched ✓		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Extra Sheet.		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,668,232 A (CORDES et al.) 26 May 1987, column 1, line 67 through column 2, line 35.	32 and 35
X	US 5,356,934 A (ROBERTSON et al.) 18 October 1994, column 2, lines 20-42.	32 and 35
X	US 5,326,570 A (RUDNIC et al.) 05 July 1994, column 1, lines 56-64.	32 and 35
X — Y	US 5,292,499 A (EVANS, et al.) 08 March 1994, column 6, lines 32-38 and 57-67; column 9, lines 1-31.	1-4, 21-24, 26, 32-36 — 5-20, 25, 27-31
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: *A* document defining the general state of the art which is not considered to be of particular relevance *B* earlier document published on or after the international filing date *I* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art *A* document member of the same patent family	
Date of the actual completion of the international search 07 JANUARY 1998	Date of mailing of the international search report 10 FEB 1998	
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer GABRIELLE PHELAN Telephone No. (703) 308-2301 	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19651

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,446,070 A (MANTELLE) 29 August 1995, column 13, lines 49-68; column 23, line 38 through column 41, line 46.	1-4, 21-24, 26, 32-36, ----- 5-20, 25, 27-31.
X,P ----- Y,P	US 5,656,286 A (MIRANDA, et al.) 12 August 1997, column 11, line 65 through column 32, line 46; column 33, lines 1-15 and 56-68; column 34, lines 38-47.	1-4, 21-24, 26, 32-36 ----- 5-20, 25, 27-31.
X,P ----- Y,P	US 5,693,337 A (SUZUKI, et al.) 02 December 1997, column 2, lines 28-47; column 5, line 15 through column 6, line 55; column 7, lines 20-27.	1-4, 21-24, 26, 32-36 ----- 5-20, 25, 27-31.

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS

transdermal, lecithin, fluoxetine, bupropion, reboxetine, carbamazepine, valproic acid, sertraline, fluvoxamine, nefazodone, trazadone, amitriptylene, propranolol, permoline, pergolide, gabapentin, bromocriptine

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- (72) Inventors; and
(75) Inventors/Applicants (for US only): HOECK, Ulla [DK/DK]; Kighusvaenget 7, DK-3400 Hillerød (DK). KREILGÅRD, Bo [DK/DK]; Smedievej 18, DK-3400 Hillerød (DK). KRISTENSEN, Helle [DK/DK]; Lindgårds Allé 16, DK-3550 Slangerup (DK).

(54) Title: TRANSDERMAL ADMINISTRATION OF REBOXETINE

(57) Abstract: Device for transdermal administration of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, to the use of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, method for the manufacturing of a medicament to be administered transdermally, and methods of treating depression and/or symptoms associated with this condition and/or for treating addictive disorders and withdrawal syndromes, adjustment disorders, age-associated learning and mental disorders, anorexia nervosa, apathy, attention-deficit disorders due to general medical conditions, attention-deficit hyperactivity disorders, bipolar disorders, bulimia nervosa, chronic fatigue syndrome, conduct disorders, cyclothymic disorders, depression, dysthymic disorders, fibromyalgia and other somatoform disorders, stress incontinence, generalized anxiety disorders, inhalation disorders, an intoxication disorders, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorders, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, psychotic disorders, seasonal affective disorder, sleep disorder, social phobia, specific developmental disorders and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome and symptoms associated with these conditions, and/or for obtaining an anti-reserpine and/or noradrenaline reuptake inhibiting effect by transdermal administration of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof.

WO 01/47503 A1

Transdermal administration of Reboxetine

Field of invention

This invention relates to a device for transdermal administration of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, to the use of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, for the manufacturing of a medicament to be administered transdermally, and to methods of treating depression and/or symptoms associated with this condition and/or for treating addictive disorders and withdrawal syndromes, adjustment disorders, age-associated learning and mental disorders, anorexia nervosa, apathy, attention-deficit disorders due to general medical conditions, attention-deficit hyperactivity disorders, bipolar disorders, bulimia nervosa, chronic fatigue syndrome, conduct disorders, cyclothymic disorders, depression, dysthymic disorders, fibromyalgia and other somatoform disorders, stress incontinence, generalized anxiety disorders, inhalation disorders, an intoxication disorders, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorders, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, psychotic disorders, seasonal affective disorder, sleep disorder, social phobia, specific developmental disorders and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome and symptoms associated with said conditions, and/or for obtaining an anti-reserpine and/or noradrenaline reuptake inhibiting effect by transdermal administration of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof.

Background

Reboxetine is the generic name of the pharmaceutical substance having the chemical name 2-(α -(2-ethoxyphenoxy)benzyl)-morpholine and its pharmaceutically acceptable salts. Reboxetine can be a free base, or it can include reboxetine methanesulfonate (also called reboxetine mesylate) or any other pharmaceutically acceptable salt that does not significantly affect the pharmaceutical activity of the substance. Reboxetine and a method of synthesis thereof are described in US 4,229,449. Methods of preparation are described in US 5,068,433 and US 5,391,735. Reboxetine is also known under the trade name EDRONAX[®].

Reboxetine is a selective and potent inhibitor of the reuptake of noradrenaline; it also has a weak effect on serotonin reuptake. Pharmacodynamic studies performed in vivo and in vitro indicate that reboxetine possesses antidepressant activity and a lower

incidence of side effects than commonly is seen with the tricyclic antidepressants. Reboxetine is highly potent, with central nervous system (CNS) effects demonstrated at doses of 1 and 3 mg. Phase II studies in patients with Major Depressive Disorders identified the non-tolerated dose in patients as 12 mg/day, which produced dose-limiting
5 hypotension. Therefore, daily doses of 8 and 10 mg were selected for subsequent development, since these doses were associated with maximal response and minimal side-effects.

Pharmacokinetic studies of reboxetine indicate that the drug is rapidly and extensively absorbed after oral administration. Soon after peak plasma levels are obtained
10 reboxetine plasma levels decay with a half-life of 12-16 hours. Unchanged drug, extensively bound to plasma proteins, is the main molecular species that is present in the systemic circulation. Clearance from the systemic circulation is mainly taking place by hepatic metabolism. The amount excreted by the renal pathway accounted for 78 % of the administered dose, of which 13 % was unchanged reboxetine.

15 Reboxetine is an equimolar mixture of two enantiomers. The pharmacokinetics of each enantiomer have been evaluated, and neither chiral inversion nor interactions between enantiomers have been observed after racemic administration.

Reboxetine has a molecular weight of 313,4 g/mol and 409,5 g/mol as the methanesulphonate salt. Reboxetine base is freely soluble in ethanol, propylene glycol,
20 ethylacetate and isopropylmyristate. It is slightly soluble in water and 0,05 M phosphate buffer, pH 7,4. The partition coefficient (Log P) between n-octanol and phosphate buffer at pH 7,4 is 0,86.

The present invention pertains to transdermal administration of reboxetine as R-isomer, S-isomer or as a racemic mixture. Properties supporting the feasibility of the
25 patch principle are that depression and symptoms associated with this condition, as well as with the other conditions mentioned above, might benefit from a flat serum concentration profile.

Prior Art

WO 99/11208 (Williams and Murdock) discloses transdermal delivery of a large
30 number of medical agents, including reboxetine, using a matrix of a lecithin gel such as a lecithin organogel. However, WO 99/11208 does not disclose transdermal delivery of reboxetine from any other transdermal system.

A number of publications disclose different devices for transdermal administration of drugs as such. Except for the captioned WO 99/11208 no such publication

though relates to transdermal delivery of reboxetine. For example US 5 811 465 discloses transdermal delivery of anti-depressive compounds, without relating at all to reboxetine.

Objects of the invention

5 A transdermal formulation with reboxetine as active ingredient will provide an alternative to the tablet formulation for the oral route. The possibility exists that due to the more constant serum concentrations during a dosage interval, side effects in comparison to immediate release tablets may be further reduced, while clinical efficacy is maintained.

10 The transdermal delivery route avoids the risk for dose dumping with extended release oral forms of administration. Moreover, patient compliance will be increased as

- elderly people and children may have difficulties in swallowing oral dosage forms,

- patients may visually observe that they are taking their medication (contrary to

15 not remembering whether they swallowed their tablet),

- once-a-day administration is possible,

- several-days administration is possible with one patch.

Overall, these effects increase convenience and compliance for patients.

Accordingly, a first object of the present invention is to provide a device for

20 transdermal administration of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, for achieving an antidepressant effect and/or for obtaining an effect in treating addictive disorders and withdrawal syndromes, adjustment disorders, age-associated learning and mental disorders, anorexia nervosa, apathy, attention-deficit disorders due to general medical conditions, attention-deficit hyperactivity disorders,

25 bipolar disorders, bulimia nervosa, chronic fatigue syndrome, conduct disorders, cyclothymic disorders, depression, dysthymic disorders, fibromyalgia and other somatoform disorders, stress incontinence, generalized anxiety disorders, inhalation disorders, an intoxication disorders, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorders, panic disorder, peripheral neuropathy, post-

30 traumatic stress disorder, premenstrual dysphoric disorder, psychotic disorders, seasonal affective disorder, sleep disorder, social phobia, specific developmental disorders and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome.

A second object of the invention is to provide a device for transdermal administration of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, for achieving an anti-reserpine effect and/or a noradrenaline reuptake inhibiting effect.

5 A third object of the invention is to provide use of a compound having an anti-depressant effect, comprising reboxetine for the manufacture of a composition to be administered transdermally for treating depression or symptoms associated with this condition and/or for treating addictive disorders and withdrawal syndromes, adjustment disorders, age-associated learning and mental disorders, anorexia nervosa, apathy, attention-deficit disorders due to general medical conditions, attention-deficit hyperac-
10 tivity disorders, bipolar disorders, bulimia nervosa, chronic fatigue syndrome, conduct disorders, cyclothymic disorders, depression, dysthymic disorders, fibromyalgia and other somatoform disorders, stress incontinence, generalized anxiety disorders, inhalation disorders, an intoxication disorders, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorders, panic disorder, peripheral
15 neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, psychotic disorders, seasonal affective disorder, sleep disorder, social phobia, specific developmental disorders and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome.

A fourth object of the invention is to provide use of a compound having an anti-
20 reserpine effect and/or a noradrenaline reuptake inhibiting effect, comprising reboxetine for the manufacture of a composition to be administered transdermally for treating conditions in need for such effects.

A fifth object of the invention is to provide a method of treating depression or symptoms associated with this condition and/or for treating addictive disorders and
25 withdrawal syndromes, adjustment disorders, age-associated learning and mental disorders, anorexia nervosa, apathy, attention-deficit disorders due to general medical conditions, attention-deficit hyperactivity disorders, bipolar disorders, bulimia nervosa, chronic fatigue syndrome, conduct disorders, cyclothymic disorders, depression, dysthymic disorders, fibromyalgia and other somatoform disorders, stress incontinence,
30 generalized anxiety disorders, inhalation disorders, an intoxication disorders, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorders, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, psychotic disorders, seasonal affective disorder, sleep disorder

der, social phobia, specific developmental disorders and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome by administering reboxetine transdermally.

A sixth object of the invention is to provide a method of treating diseases, in humans or animals, which are treatable with anti-reserpine agents and/or noradrenaline uptake inhibiting agents by administering reboxetine transdermally.

Other objects of the invention will become apparent to one skilled in the art, and still other objects will become apparent hereinafter.

Summary of the invention

The present invention relates to transdermal administration of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof for achieving an antidepressant effect and/or an anti-reserpine effect and/or a noradrenaline reuptake inhibiting effect. Said effects are primarily achieved through the systemic effect of reboxetine. Anyhow other actions are not excluded.

Brief description of the drawings

Figures 1A – 1D are schematic drawings of different types of devices for transdermal delivery of drugs.

Figure 2 is a diagram showing *in vitro* skin permeation of reboxetine base from saturated solutions, according to Example 1.

Figure 3 is a diagram showing *in vitro* skin permeation of 5 % reboxetine base solutions, according to Example 2 and Example 3.

Figure 4 is a diagram showing *in vitro* skin permeation across synthetic membranes from 5 % reboxetine base solutions, according to Example 4.

Figure 5 is a diagram showing *in vitro* skin permeation of reboxetine base from different transdermal systems, according to Example 6.

Figure 6 is a diagram showing *in vitro* skin permeation of reboxetine base from different transdermal systems, applying human skin, according to Example 7.

Figures 7 and 8 are diagrams showing *in vitro* dissolution of reboxetine base from different transdermal systems, according to Example 8.

Figure 9 is a diagram showing *in vitro* skin permeation of different concentrations of reboxetine base from a transdermal system, according to Example 10.

Figure 10 is a diagram showing *in vitro* dissolution of reboxetine base from reservoir patches, according to Example 12.

Figure 11 is a diagram showing *in vitro* skin permeation of 5 % reboxetine methanesulphonate solutions, according to Example 13 and Example 14.

Figure 12 is a diagram showing *in vitro* skin permeation of reboxetine methane-sulphonate from different transdermal systems according to Example 16.

Figure 13 is a diagram showing *in vitro* skin permeation of reboxetine methane-sulphonate enantiomers from different transdermal systems, according to Example 18.

5 Figure 14 is a diagram showing *in vitro* dissolution of reboxetine methanesulphonate enantiomers from different transdermal systems, according to Example 19.

Detailed description of the invention

Transdermal delivery of drugs can be achieved from topical products such as ointments or cremes or from transdermal devices. The present invention primarily re-
10 lates to administration via transdermal devices, which usually are called transdermal patches. But other forms for topical administration, such as creams and ointments are also included.

Devices usable as transdermal patches can be categorized in many different ways. A comprehensive categorization of transdermal devices is found in Wick S. De-
15 veloping A Drug-In-Adhesive Design for Transdermal Drug Delivery. Adhe Age 1995; 38: 18-24.

Wick essentially divides transdermal devices into the below four main groups:

- the reservoir type, in which the drug is placed in a liquid or a gel and delivered across a rate-moderating membrane to the skin;
- 20 - the matrix type, in which the drug is placed within a non-adhesive polymeric material, typically a hydrogel or soft polymer;
- the drug-in-adhesive type, in which the drug is placed within an adhesive polymer;
- the multi-laminate type, which is similar to the drug-in-adhesive design but
25 which incorporates an additional layer of pressure sensitive adhesive to cover the entire device and affix it to the skin. A membrane can also be incorporated into this multi-laminate type as shown in Fig. 1B.

The above four main types of transdermal devices are schematically illustrated in Fig. 1A - 1D.

30 A fifth important type, not mentioned by Wick, is the iontophoretic type, which is the predominant mechanism for electrically assisted transdermal delivery. When using the iontophoretic type, an electrical potential gradient is used for transferring the drug through the skin - see further e.g. Singh P et al. Iontophoresis in Drug Delivery: Basic Principles and Applications. Crit Rev Ther Drug Carrier Syst 1994; 11: 161-213.

Besides this, electroporation, electroosmosis, electroincorporation and jet injection can be used.

Electroporation is the creation of transient aqueous pores in lipid bilayer membranes by the application of a short (msec) electric pulse (Prausnitz MR et al. Proc Int Symp Control. Rel Biact Mater 1993; 20: 95-96). By using electroporation the skin permeability will be altered such that resistance to drug transport is reduced. Electroporation has been employed in transdermal drug delivery by coupling it with iontophoresis (Bommannan D et al. Pharm Res 1994; 11: 1809-1814, Prausnitz MR et al. Proc Na Acad Sci USA 1993; 90: 10504-10508, and Riviere JE et al. J Controlled Release 1995; 36: 299-233). In these cases, a short (few milliseconds) pulse of high voltage alters the skin permeability such that subsequent iontophoresis is facilitated.

With electroosmosis the electric field creates a convective flow of water which allows hydrophilic compounds to be transported. Closely related to electroporation is electroincorporation but here particles (microspheres, liposomes) are placed on the surface of the skin and subsequent high voltage electrical pulses are employed (Riviere JE and Heit MC. Pharm Res 1997; 14: 687-697).

Jet injection can be used both for powders and liquids (Muddle AG et al. Proc Int Symp Control. Rel Biact Mater 1997; 24: 713-714, and Seyam RM et al. Urology 1997; 50: 994-998. By using jet injection a drug can be administered by a no-needle painless injection.

The above split-up into groups is not very strict as variations and combinations of each may be envisaged. So may a multi-laminate type device encompass a device with many layers in a sandwich construction, such as the drug in one layer, excipients such as enhancers in a further layer, a membrane in another layer and an adhesive in still another layer. Or it could be composed of several drug-in-adhesive layers or combinations of the above layers.

The liquid or gel used in the above reservoir type device could be hydrophilic or lipophilic, such as water, alcohols, mineral oils, silicone fluids, various copolymers, such as ethylene vinyl acetate, vinyl acetate or polyvinyl alcohol/polyvinyl pyrrolidone. The reservoir may also include dyes, inert fillers, diluents, antioxidants, antiirritants, antisensitizers, permeation enhancers, stabilizers, solubilizing agents and other pharmacologically inactive pharmaceutical agents being well known in the art.

The adhesives used are generally of three types, being the rubber type, encompassing inter alia polyisobutylenes, the acrylate type and the silicone type. The adhesiv-

es may be chemically modified, and may have a wide range of molecular weights. To the adhesive could be added several types of excipients such as fillers, stabilizers, plasticizers, buffering agents, permeation enhancers, permeation retarders, antiirritants, antisensitizers, solubilizing agents and other pharmaceutical ingredients being well known in the art.

Polymer films that may be used for making the rate-moderating membrane include, without limitation, those comprising low- and high-density polyethylene, ethyl vinyl acetate copolymers and other suitable polymers.

The backing layer serves the purposes of preventing passage of the drug and/or environmental moisture through the outer surface of the patch, and also for providing support for the system, where needed. Further the backing layer can provide occlusion, and thus increasing the rate of delivery of the drug into the skin. The backing layer may be chosen so that the end product is appealing to the users, whether children, adults, elderly people or other customer groups. The backing layer is impermeable to the passage of reboxetine or inactive ingredients being present in the formulation and can be flexible or nonflexible. Suitable materials include, without limitation, polyester, polyethylene terephthalate, some type of nylon, polypropylene, metallized polyester films, polyvinylidene chloride and aluminium foil.

The release liner can be made of the same materials as the backing layer.

As will be clear further below the invention according to the present application encompasses administration of reboxetine via all hitherto known types of devices for transdermal administration. Mainly the above categorization will be adhered to in this application. Anyhow this does not exclude that transdermal devices which might fit better according to some other categorization also are included in the present invention.

It is well known in the art that the properties of the skin as such influence the permeation of the drug through the skin into the systemic circulation. It could thus be said that the skin controls the drug permeation rate. Anyhow as the skin as such is no part of the present invention the behaviour of the skin in connection with transdermal drug delivery will not be discussed in detail. It is also well accepted in the art that when rate-controlling properties are attributed to a transdermal device is meant properties associated with the release rate from the device as such. It is also evident that when a transdermal device is designed to exhibit a certain release performance the properties of the skin need be taken into consideration during the design process.

Hydrogels (used for the matrix type and reservoir transdermal systems) are materials, which swell when placed in excess water. They are able to swell rapidly and retain large amount of water in their swollen structure. The materials do not dissolve in water and maintain three-dimensional networks. Hydrogels are usually made of hydrophilic polymer molecules that are crosslinked either by chemical bonds or other cohesion forces such as ionic interaction, hydrogen bonding or hydrophobic interaction. Hydrogels are elastic solids in the sense that there exist remembered reference configurations to which the system returns even after being deformed for a very long time (Park K et al. Biodegradable Hydrogels for Drug Delivery. Technomic Publishing Co., Inc. 1993). Examples of hydrogels are polyvinylpyrrolidone and cellulose hydrogels such as methylcellulose, hydroxyethylcellulose, hydroxyethylmethylcellulose, carboxymethylcellulose, ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose and microcrystalline cellulose (colloidal). Other examples are: Guar gum, gum arabic, agar, tragacanth, carrageenan, xanthan gum, algin, carbomer, dextran and chitin.

Also it could be possible to manufacture a polymer-system with no foils (backing membrane and release liner) consisting of 1, 2 or more polymers in a solvent and added drug and e g plasticizers and enhancers. The polymers could be a blend of hydrophilic and hydrophobic species. This product should be applied to the skin using an appropriate device where the solvent evaporates and leaving a thin invisible film. This type of systems can also be of a multilayer type where the drug could be incorporated in different layers of polymers with different release characteristics and/or alternative layers without drug that could act as a rate limiting membrane. The outer layer is most preferable hydrophobic to obtain occlusion.

The rate control ability is often a very important feature for a transdermal device in order to deliver the correct amount of drug to the patient at the correct time. Thereby maximum efficacy is achieved while side effects are minimized. Many factors influence the rate control ability of a transdermal device. In the below Table 1 the most important such factors are listed and their influence in the respective device type is marked. A plus sign indicates that the influence is strong. The absence of a plus sign does not exclude that the corresponding factor has at least some influence.

Table 1. Type of device

Factor	Reservoir	Matrix	Drug-in-adhesive	Multilaminate
Polymer type(s)	+	+	+	+
Modification of the polymer(s)		+	+	+
Activity, i.e. concentration, of drug e.g. supersaturation	+	+	+	+
Additives in polymer(s)				
- Enhancer(s)	+	+	+	+
- Cyclodextrine(s)	+	+	+	+
- Retarder(s)	+	+	+	+
pH-adjustment	+	+	+	+
Solubilizer(s)	+	+	+	+
Emulsifier(s)	+	+	+	+
Membrane(s)				
- Hydrophilic	+			
- Lipophilic	+			
- Thickness	+			
- Pore size	+			
- Density	+			
Chemical stabilizer(s)	+	+	+	+

Taking into account the convenience of wearing a patch as well as ease of manufacturing, the drug-in-adhesive and the reservoir type device are presently considered to be the best modes for carrying out the present transdermal delivery of reboxetine.

It may also be desired to include, at least in some device types, one or more transdermal permeation enhancing substance(s) in order to increase the amount of reboxetine which may permeate the skin and reach the systemic circulation, or in order to reduce the size of the patch. Enhancers suitable in the present invention may be categorized in the below groups, although enhancers not belonging to any of these groups are not excluded.

- alcohols, such as short chain alcohols, e.g. ethanol and the like, long chain fatty alcohols, e.g. lauryl alcohols, and the like, and polyalcohols, e.g. propylene glycol, glycerin and the like;

- amides, such as amides with long aliphatic chains, or aromatic amides like N,N-diethyl-m-toluamide;

- amino acids;

- azone and azone-like compounds;

5 - essential oils, i.e. essential oils or constituents thereof, such as l-carvone, l-menthone-menthol, and the like;

- fatty acids and fatty acid esters, such as oleic acid, lauric acid and the like, further esters of fatty acids, such as isopropyl myristate, and various esters of lauric acid and of oleic acid and the like;

10 - macrocyclic compounds, such as cyclopentadecanone and cyclodextrins;

- phospholipid and phosphate compounds, such as phospholipids;

- 2-pyrrolidone compounds; and

- miscellaneous compounds, like sulfoxides, such as dimethyl sulfoxides, and fatty acid ethers, such as Laureth-9 and polyoxylaurylether.

15 Combinations of enhancers from different groups in the above categorization may prove very useful and efficient.

For overview of enhancers, see further e.g. Santus GC et al. Transdermal enhancer patent literature. J Control Release 1993; 25: 1-20, and Smith EW et al. Percutaneous penetration enhancers. CRC Press Inc. 1995.

20 Detailed description of the invention.

The following examples are intended to illustrate, but not to limit the scope of the invention, although the embodiments named are of particular interest for our intended purposes.

Apparatus used in the examples

25 As disclosed below.

Materials

As disclosed below.

Drug

30 Reboxetine methanesulphonate was supplied by Pharmacia & Upjohn (Kalama-zoo, USA).

Polymers

Eudragit E 100 aqueous and organic based were supplied by Röhm GmbH Chemische Fabrik, Polyethylene glycol 400 (PEG 400) was supplied by Merck-Schuchardt, Polyvidone 90 (PVP 90) was supplied by BASF, MA-24 was from Adhesive

Research Inc., Durotak 387-2287, 387-2516 and 387-2852 were supplied by National Starch & Chemical.

Foils

Drug-in-adhesive patch: The siliconized polyester release liner (FL2000-75 PET 1S) was obtained from Rexam Release and the pigmented occlusive backing membrane (Scotchpak 1109) was obtained from 3M Corp.

Reservoir patch: 3M backing membrane (Scotchpak 9732), 3M release liner (Scotchpak 9733), plus the rate controlling membranes; CoTran membranes (with 9 %, 19 % and 28 % vinyl acetate (VA)) were all from 3M Corp.

Other materials

Azone was obtained from Discovery Therapeutics Inc., Methyllaurat was supplied by Fluka.

Other chemicals used were of analytical grade.

Patch formulation studies

Patch formulations were prepared by adding reboxetine base to each of the chosen polymers (acrylates, polyisobutylenes, PVP/PEG). The drug gels were coated onto a siliconized polyester release liner (FL2000-75 PET 1S) by using a coating equipment (Lab Drawdown Coater, Type LC-100) The laminates were dried and having a dry coat weight of approximately 100 g/m². A backing membrane (Scotchpak 1109) was laminated onto the dried drug gel, resulting in a drug-in-adhesive laminate. Patches were die-cut from the finished sheet, pouch-packed in Barex foil and stored at room temperature until use. Any deviation from the above will be mentioned under the individual examples.

Reservoir patch formulation study

5 % reboxetine base was dissolved in ethanol and 5 % reboxetine methanesulphonate was dissolved in water. The solutions were thereafter filled in reservoir patches by use of a reservoir patch machine (A&D, GmbH, Type PF-80). As backing membrane Scotchpak 9732 was used and as release liner Scotchpak 9733 was used. The rate controlling membranes consisted either of CoTran 9702 (9 % vinyl acetate) or CoTran 9728 (19 % vinyl acetate).

Quantitative HPLC-determination of reboxetine content

The content of reboxetine was determined using a HPLC method. The system consisted of a HP 1100 pump or the equivalent, a HP1100 autosampler or the equivalent with a 20 µl loop, a HP1100 detector or the equivalent and a HP Chemstation integrator

or the equivalent. The column was Nuclosil 5C8, 150 x 4,6 mm and the mobile phase was a mixture of 0,1 M phosphate buffer pH 3,0 – acetonitrile (70+30). The flow was 1,0 ml/min and the detection wavelength was 280 nm.

In vitro dissolution studies

5 *In vitro* dissolution studies were performed by using a modified USP Type 5 paddle apparatus. The apparatus was modified by the use of a convex screen to hold the transdermal system in position during testing. The system consisted of a Pharma Test Type PTW SIII C six-vessel dissolution apparatus connected to a Pharma Test Type PTFCH Fraction collector or equivalent. As dissolution medium was used 0,05 M phosphate buffer, pH 7,4 equilibrated to 32°C. Samples were withdrawn at certain time intervals, and the amount of reboxetine was determined by HPLC. Amount of drug permeated per cm² was plotted as a function of time.

In vitro skin permeation studies

15 *In vitro* skin permeation results were obtained from studies on pig or human skin using Franz diffusion cells. Using a dermatome (Zimmer Electric Dermatome 8821, Zimmer Chirurgie) isolated 765 µm skin.

20 The skin was mounted in the diffusion cells with an available diffusion area of 1,8 cm². The inner side of the epithelium was exposed to 12,1 ml receptor phase (0,05 M phosphate buffer, pH 7,4) at 37±1°C, corresponding to 32°C on the donor side of the skin. Samples were withdrawn periodically from the receptor phase up to 48 hours and immediately replaced by fresh receptor phase. The cumulated amount of reboxetine in the receptor phase divided by skin area was plotted as a function of time. Fluxes (µg/cm²/h) were obtained by linear regression of data at steady state. The quantitative determination of reboxetine was performed using a HPLC method. Pigskin was
25 applied for all *in vitro* skin permeation studies except for Example 7.

Examples

Example 1

In vitro skin permeation studies from saturated solutions of reboxetine base.

Solution 1

30 Reboxetine base was dissolved in water equal to 6,6 mg/ml.

Solution 2

Reboxetine base was dissolved in propylene glycol equal to 280 mg/ml.

Solution 3

Reboxetine base was dissolved in ethanol equal to 344 mg/ml.

Solution 4

Reboxetine base was dissolved in isopropylmyristate equal to 119 mg/ml.

In vitro skin permeation of reboxetine base from solution 1 to 4 through dermatomed pig skin, 765 μm was investigated using Franz diffusion cells. The cumulative amount of reboxetine base in the receptor solution versus time is shown in Fig. 2. An increase in the amount of reboxetine base permeated is seen in the following order: isopropylmyristate > ethanol > propylene glycol > water. The results show that is possible to adjust the flux through the skin by changing the solvent. It is further obvious that varying the concentration of reboxetine in accordance with Ficks first law can alter the flux.

Example 2

In vitro skin permeation studies of 5 % reboxetine base solutions.

Solution 5

5 % reboxetine base dissolved in ethanol.

Solution 6

5 % reboxetine base dissolved in propylene glycol.

In vitro skin permeation of reboxetine base from solution 5 and 6, respectively through dermatomed pig skin, 765 μm , was investigated using Franz diffusion cells. The cumulative amount of reboxetine base in the receptor solution versus time is shown in Fig. 3. An increase in the amount of reboxetine base permeated is seen in the following order: ethanol > propylene glycol. The results show that it is possible to adjust the flux through the skin by changing the solvent.

Example 3

In vitro permeation studies from solutions of 5 % reboxetine base added enhancers.

Solution 7

5 % reboxetine base dissolved in ethanol, added 5 % Azone.

Solution 8

5 % reboxetine base dissolved in ethanol, added 5 % Methyllaurat.

In vitro skin permeation of reboxetine base from solution 7 and 8, respectively, through dermatomed pigskin, 765 μm , was investigated using Franz diffusion cells. The cumulative amount of reboxetine base in the receptor solution versus time is shown in Fig. 3. An increase in the amount of reboxetine base permeated is seen in the following

order: Methyllaurat > Azone. The results show a significant increase in flux of reboxetine base when enhancer is added the solutions.

Example 4

5 *In vitro* skin permeation studies across synthetic membranes and dermatomed pigskin, 765 μm , from 5 % reboxetine base solutions, simulating the reservoir type transdermal device.

Solution 9

5 % reboxetine base dissolved in ethanol.

Solution 10

10 5 % reboxetine base dissolved in propylene glycol.

In vitro skin permeation of reboxetine base from solution 9 and 10, respectively, across 3 different synthetic membranes was investigated using Franz diffusion cells.

Membranes of the following types were used: CoTran 9702 (microporous polyethylene film) with 9 % vinylacetate (VA), CoTran 9728 with 19 % vinylacetate and an
15 experimental CoTran membrane with 28 % vinylacetate. The three mentioned CoTran membranes were applied to solution 9, whereas only CoTran (19 % VA) and CoTran (28 % VA) were applied to solution 10. The membranes were placed on top of dermatomed pigskin. *In vitro* skin permeation of reboxetine base from solution 9 and 10, through dermatomed pig skin, 765 μm , was investigated using Franz diffusion cells.
20 The cumulative amount of reboxetine base in the receptor solution versus time is shown in Fig. 4. The membranes impede the flux of reboxetine base considerably; increased flux is observed with increased amount of VA in the membranes. The results show that it is possible to control the permeation rate of reboxetine base from a reservoir type device by changing the membrane.

25 Example 5

System 1 (drug-in-adhesive, acrylate)

Loading of different Durotak acrylates with reboxetine base.

Patches containing approximately 1 mg/cm² reboxetine base in Durotak 387-2287, 387-2516 and 387-2852 were manufactured according to the "patch formulation
30 studies" described previously. The drug gels were coated and dried at 80°C for 10 min., resulting in a dry coat weight of approximately 100 g/m².

System 2 (drug-in-adhesive, hydrophilic matrix)Loading of hydrophilic matrix with reboxetine base

5 A patch containing approximately 1 mg/cm² reboxetine base in a mixture of polyvidone 90 : polyethylene glycol 400 (1:1) was manufactured. Reboxetine base, polyvidone 90 and polyethylene glycol 400 were dissolved in ethanol 99,9 %. The drug gel was coated and dried at 50°C for 4 hours, resulting in a dry coat weight of approximately 100 g/m².

System 3 (drug-in-adhesive, polyisobutylene)Loading of polyisobutylene with reboxetine base

10 A patch containing approximately 1 mg/cm² reboxetine base in MA-24 was manufactured. The drug gel was coated and dried at 80°C for 10 min, resulting in a dry coat weight of approximately 100 g/m².

System 4 (drug-in-adhesive, methacrylate).Loading of Eudragit methacrylate with reboxetine base.

15 A patch containing approximately 1,05 mg/cm² reboxetine base in Eudragit E 100, organic based. 2,9 g of reboxetine base was added to 40 g of Eudragit E 100, organic based. The drug gel was coated and dried at 60°C for 10 min, resulting in a dry coat weight of approximately 100 g/m².

Example 6

20 *In vitro* skin permeation studies of the transdermal drug delivery System 1, 2, 3 and 4 according to Example 5 (Fig. 5).

In vitro skin permeation of reboxetine base through dermatomed pig skin, 765 µm was investigated using Franz diffusion cells. The cumulative amount of reboxetine base in the receptor solution versus time is shown in Fig. 5. Fluxes are in the
25 range of 0 – 15,8 µg/cm²/h. It appears that different fluxes can be obtained by applying different polymers.

Example 7

In vitro skin permeation studies applying human skin.

In vitro skin permeation studies of the transdermal drug delivery System 1 (Durotak 387-2287) and 2 (polyvidone90:polyethylene glycol400) according to Example 5
30 (Fig. 6).

In vitro skin permeation of reboxetine base through dermatomed human skin, 765 µm was investigated using Franz diffusion cells. The cumulative amount of reboxetine base in the receptor solution versus time is shown in Fig.6. Fluxes are in the

range of 7,1 – 18,9 $\mu\text{g}/\text{cm}^2/\text{h}$. Higher fluxes is obtained when applying human skin compared to applying pig skin.

Example 8

Stability studies were carried out on the transdermal drug delivery Systems 1 (Durotak 387-2287 and Durotak 387-2852) according to Example 5. The patches were stored at 25°C/60 % R.H. and 40°C/75 % R.H.

Quantitative determination of reboxetine base was done by HPLC after 0, 1, 2 and 3 months of storage. (Table 2). Likewise was *in vitro* dissolution studies performed at 0, 1, 2 and 3 months of storage (Fig. 7 and 8). From Table 2 it appears that the quantitative amount of reboxetine base after storage is consistent with the initial value, and no degradation has occurred. When comparing the release profiles in Fig. 7 and 8 it is apparent that no change in release has occurred after storage. Furthermore it is seen that using different polymers can alter the release profile.

Below Table 2 shows quantitative determination of reboxetine base after 0, 1, 2 and 3 months of storage, according to Example 8.

Table 2 Stability of reboxetine base in different Durotak polymers

Concentration 1 mg/cm^2

Coat weight 100 g/m^2

Storage time	Temp. 25°C 60 % R.H.		Temp. 40°C 75 % R.H.	
	Durotak 2852 Reboxetine base (mg/cm^2)	Durotak 2287 Reboxetine base (mg/cm^2)	Durotak 2852 Reboxetine base (mg/cm^2)	Durotak 2287 Reboxetine base (mg/cm^2)
Zero	0,72	0,83	0,72	0,83
1 month	0,75	0,84	0,76	0,78
2 months	0,76	0,78	0,67	0,72
3 months	0,79	0,79	0,78	0,72

20

Example 9

System 5 (drug-in-adhesive, acrylate)

Loading of acrylate with reboxetine base in different concentrations (same dry coat weight).

Patches containing approximately 0,7 mg/cm^2 , 1,05 mg/cm^2 and 1,4 mg/cm^2 reboxetine base in Durotak 387-2287 were manufactured according to the "patch formu-

25

lation studies" described previously. The drug gels were coated and dried at 80°C for 10 min, resulting in a dry coat weight of approximately 140 g/m².

Example 10

5 *In vitro* skin permeation studies of the transdermal drug delivery System 5 according to Example 9 (Fig. 9).

In vitro skin permeation of reboxetine base through dermatomed pig skin, 765 µm was investigated using Franz diffusion cells. The cumulative amount of reboxetine base in the receptor solution versus time is shown in Fig. 9. Fluxes are in the
10 range of 1,6 – 2,9 µg/cm²/h. It is seen that the highest flux is obtained from the patch having the highest drug load of reboxetine base. However, no clear correlation between the medium and minimum drug load, and permeated amount of reboxetine base is evident from Fig. 9.

Example 11

15 System 6 (reservoir patch)

 5 % reboxetine base dissolved in ethanol. 750µl were filled in each reservoir patch using the reservoir machine. As backing membrane Scotchpak 9732 was used and as release liner Scotchpak 9733 was used. Two different rate controlling membranes were used, CoTran 9702 with 9 % vinyl acetate and CoTran 9728 with 19 % vinyl acetate.
20 No adhesive was applied to the reservoir patch.

Example 12

In vitro dissolution studies of the transdermal drug delivery System 6, according to Example 11 (Fig. 10).

 Reservoir patches of 20,4 cm² were applied to the disk assembly, using a suitable adhesive with the release surface facing up. Samples were withdrawn periodically
25 up to 24 hours. The amount of reboxetine base released from the patches was expressed in mg reboxetine base per cm². The results show that only a relatively small amount of reboxetine base is released from the reservoir patches. A decreased release is observed with decreased amount of VA in the CoTran membranes. The results show that it is
30 possible to control the release rate of reboxetine base from a reservoir type device by changing the CoTran membrane or any other membranes applied.

Example 13

In vitro skin permeation studies of 5 % reboxetine methanesulphonate solutions

Solution 11

5 % reboxetine methanesulphonate dissolved in water.

Solution 12

5 % reboxetine methanesulphonate dissolved in propylene glycol.

- 5 *In vitro* skin permeation of reboxetine methanesulphonate from solution 11 and 12, respectively, through dermatomed pigskin, 765 μm , was investigated using Franz diffusion cells. The cumulative amount of reboxetine methanesulphonate in the receptor solution versus time is shown in Fig. 11. An increase in the amount of reboxetine methanesulphonate permeated is seen in the following order: water > propylene glycol.
- 10 The results show that it is possible to adjust the flux through the skin by changing the solvent. The results also show that surprisingly it is possible to use reboxetine methanesulphonate and still obtain useful fluxes.

Example 14

- 15 *In vitro* permeation studies from solutions of 5 % reboxetine methanesulphonate added enhancers.

Solution 13

5 % reboxetine methanesulphonate dissolved in water, added 5 % Azone.

Solution 14

- 20 5 % reboxetine methanesulphonate dissolved in propylene glycol, added 5 % Methyllaurat.

- 25 *In vitro* skin permeation of reboxetine methanesulphonate from solution 13 and 14, respectively, through dermatomed pigskin, 765 μm , was investigated using Franz diffusion cells. The cumulative amount of reboxetine methanesulphonate in the receptor solution versus time is shown in Fig. 11. An increase in the amount of reboxetine methanesulphonate permeated is seen in the following order: Azone > Methyllaurate. The results show a significant increase in flux of reboxetine methanesulphonate when enhancer is added to the solutions.

Example 15System 7 (drug-in-adhesive, acrylate)

- 30 Loading of Durotak acrylate with reboxetine methanesulphonate

A patch containing approximately 1 mg/cm^2 reboxetine methanesulphonate in Durotak 387-2287 was manufactured according to the "patch formulation studies" described previously. The drug gels were coated and dried at 80°C for 10 min., resulting in a dry coat weight of approximately 100 g/m^2 .

System 8 (drug-in-adhesive, hydrophilic matrix)Loading of hydrophilic matrix with reboxetine methanesulphonate

A patch containing approximately 1 mg/cm² reboxetine methanesulphonate in a mixture of polyvidone 90 : polyethylene glycol 400 (1:1) was manufactured. Reboxetine methanesulphonate, polyvidone 90 and polyethylene glycol 400 were dissolved in ethanol 99,9 %. The drug gel was coated and dried at 50°C for 4 hours, resulting in a dry coat weight of approximately 100 g/m².

System 9 (drug-in-adhesive, methacrylate)Loading of Eudragit methacrylate with reboxetine methanesulphonate.

A patch containing approximately 1 mg/cm² reboxetine methanesulphonate in Eudragit E 100, aqueous based, was manufactured. The drug gel was coated and dried at 60°C for 10 min, resulting in a dry coatweight of approximately 100 g/m².

Example 16

In vitro skin permeation studies of the transdermal drug delivery System 7, 8 and 9 according to Example 15 (Fig. 12).

In vitro skin permeation of reboxetine methanesulphonate through dermatomed pig skin, 765 µm was investigated using Franz diffusion cells. The cumulative amount of reboxetine methanesulphonate in the receptor solution versus time is shown in Fig. 12. Fluxes are in the range of 0,9 – 6,6 µg/cm²/h. It appears that different fluxes can be obtained by applying different polymers.

Example 17System 10 (drug-in-adhesive, methacrylate)Loading of Eudragit methacrylate with reboxetine methanesulphonate enantiomers

A: Patch containing approximately 0,75 mg/cm² (racemic) reboxetine methanesulphonate in Eudragit E 100, aqueous based. The drug gel was coated and dried at 60°C for 10 min, resulting in a dry coat weight of approximately 75 g/m².

B: Patch containing approximately 0,75 mg/cm² (S,S (+)enantiomer) reboxetine methanesulphonate in Eudragit E 100, aqueous based. The drug gel was coated and dried at 60°C for 10 min, resulting in a dry coat weight of approximately 75 g/m².

C: Patch containing approximately 0,75 mg/cm² (R,R (-)enantiomer) reboxetine methanesulphonate in Eudragit E 100, aqueous based. The drug gel was coated and dried at 60°C for 10 min, resulting in a dry coat weight of approximately 75 g/m².

Example 18

In vitro skin permeation studies of the transdermal drug delivery System 10 (A, B and C) according to Example 17 (Fig. 13).

In vitro skin permeation of enantiomers of reboxetine methanesulphonate through dermatomed pig skin, 765 μm was investigated using Franz diffusion cells. The cumulative amount of reboxetine methanesulphonate enantiomers in the receptor solution versus time is shown in Fig. 13. Fluxes are in the range of 5,3 – 7,4 $\mu\text{g}/\text{cm}^2/\text{h}$. The enantiomers show no noticeable difference in skin permeation rate, which means that the individual enantiomers can be used in the transdermal formulations

Example 19

In vitro dissolution of the transdermal drug delivery System 10 (A, B, and C) according to Example 17 (Fig. 14).

Patches of 10 cm^2 were applied to the disk assembly, using a suitable adhesive with the release surface facing up. Samples were withdrawn periodically up to 24 hours. The amount of reboxetine methanesulphonate enantiomers released from the patches was expressed in mg reboxetine methanesulphonate per cm^2 . From Fig. 14 no difference in release profiles from the different enantiomers is observed.

Example 20

Primary skin irritation study in rabbit and test for delayed contact hypersensitivity using the Buehler test (performed by Scantox, Denmark).

The primary skin irritating effect of reboxetine methanesulphonate was investigated according to the method in the OECD Guideline No. 404, "Acute Dermal Irritation/Corrosion", 1992 and EEC Guideline B.4 "Acute Toxicity (skin irritation)", 29.12.1992.

0,5 g of reboxetine methanesulphonate moistened with approximately 0,3 ml 0,9 % NaCl was applied on 3 rabbits. After 4 hours of exposure reboxetine methanesulphonate was removed and the skin was examined 1, 24, 48 and 72 hours after termination of exposure. For reboxetine methanesulphonate the mean score for both erythema and oedema was 0.0. According to this reboxetine methanesulphonate was not classified as skin irritating.

The dermal sensitising potential of reboxetine methanesulphonate was investigated according to one of the methods recommended in the OECD Guideline NO. 406, "Skin Sensitisation, Description of the Buehler test method", 1992 and the EEC Direc-

tive published in: "Official Journal of the European Communities" No: L 383A, volume 35, 29.12.1992, part B6: Skin Sensitisation, the Buehler test.

0,1 g reboxetine methanesulphonate moistened with 0,3 ml 0,9 % NaCl was selected for the dermal inductions and for the challenge. It was concluded that no evidence of delayed contact hypersensitivity was seen after treatment with reboxetine methanesulphonate.

A iontophoretic type device may be manufactured essentially according to embodiments disclosed in e.g. Parminder Singh et al, "Iontophoresis in Drug Delivery: Basic Principles and Applications", Critical Reviews in Therapeutic Drug Carrier Systems, 1994; 11 (2&3):161-213. The administration of reboxetine or derivatives thereof is not disclosed in this reference. Anyhow it lies within the present invention to modify, using the disclosure in the present application, the embodiments according to said reference to become suitable for the administration of reboxetine.

The above examples show that it is possible to administer reboxetine and to control its release rate using all known types of devices for transdermal drug administration.

Various carriers and vehicles for reboxetine may be used in the transdermal administration. One such carrier is cyclodextrine, especially β -cyclodextrine. Reboxetine can be bound in the cavities of cyclodextrines to form so called inclusion complexes. Binding reboxetine to a cyclodextrine leads either to increased delivery rate or to decreased delivery rate depending on the reboxetine-cyclodextrine ratio.

Dosage

In the Investigator's Brochure on reboxetine is stated that for dose-response, selection of reboxetine dose regimens for oral intake was accomplished in an early phase II, non-randomized, dose-finding study, which was adequate for finding the daily dose associated with intolerance (12 mg/day) and the daily doses associated with minimal side-effect and maximal response rate 8 and 10 mg/day), although in view of the non-randomized conditions no conclusions about dose-response could be drawn.

From the above findings it is relevant to conclude that a useful dosage of transdermally administered reboxetine according to the present invention for the conditions stated above would preferably range from 0.1 mg/day to 20 mg/day. Thereby is not excluded that also lower and higher daily dosages would be useful. The exact amounts should be determined in accordance with acknowledged principles, taking into account age, weight, condition to be treated and other relevant parameters.

The data of Fig. 13 show that an apparent 0-order delivery of reboxetine through the skin takes place from about 5 to 48 hours. This 0-order delivery may continue for at least up to a week. Such a once-weekly patch will greatly improve patient compliance, which is important for patients, which often use tolterodine.

5 It should therefore also be contemplated that a device for transdermal delivery during 2 or more days would further facilitate the use of the transdermal formulation. It is possible to design a device delivers reboxetine for a predefined period of time, preferably 12, 24 or 48 hours, or even up to 7 or 14 days.

It might be desirable to use higher dosages of reboxetine during the day or night.
10 It is within the present invention to administer reboxetine in such a way that a therapeutically effective systemic level of reboxetine prevails to a higher extent during the day or the night. The above object is achievable by applying the transdermal device at the appropriate time during day or night in combination with designing the device with the appropriate release profile. The same rules for a device designed to deliver reboxetine to
15 a lower extent during the day or the night.

When reboxetine is administered in a transdermal device the latter should preferably be occlusive, which means that the device does not permit water to migrate outwardly from the skin area covered by the device or at least with a lower rate than the rate of the skins ordinary transepidermal water loss. Thereby the hydration of the skin is
20 increased which favors the penetration of reboxetine through the skin.

For convenience and/or in order to achieve a more rapid increase in plasma level it is possible to design a set of formulations of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, which comprises at least one device for transdermal delivery and at least one formulation for oral, sublingual, buccal, nasal, pulmonary, rectal and/or other transmucosal administration.
25 nary, rectal and/or other transmucosal administration.

In all the different embodiments of the present invention reboxetine may be present in just one of its above-presented forms or as a mixture of two or more forms.

CLAIMS

1. Device for transdermal administration, characterized in that it administers reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s), to a human being or an animal.

2. Device for transdermal administration, characterized in that it administers reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s), to a human being or an animal and that it is devoid of a matrix comprising lecithin gel.

3. Device for transdermal administration according to claim 1 or 2, characterized in that it administers reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s), to a human being or an animal in order to achieve an antidepressant effect for treating depression or symptoms associated with this condition.

4. Device for transdermal administration according to claim 1 or 2, characterized in that it administers reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s), to a human being or an animal in order to achieve an effect for treating addictive disorders and withdrawal syndromes, adjustment disorders, age-associated learning and mental disorders, anorexia nervosa, apathy, attention-deficit disorders due to general medical conditions, attention-deficit hyperactivity disorders, bipolar disorders, bulimia nervosa, chronic fatigue syndrome, conduct disorders, cyclothymic disorders, depression, dysthymic disorders, fibromyalgia and other somatoform disorders, stress incontinence, generalized anxiety disorders, inhalation disorders, an intoxication disorders, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorders, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, psychotic disorders, seasonal affective disorder, sleep disorder, social phobia, specific developmental disorders and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome, or symptoms associated with said conditions.

5. Device for transdermal administration according to claim 1 or 2, characterized in that it administers reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable car-

rier(s), to a human being or an animal in order to achieve an anti-reserpine effect and/or a noradrenaline reuptake inhibiting effect.

6. Device for transdermal administration according to anyone of claims 1 - 5, characterized in that reboxetine essentially is in its R-isomeric form.

5 7. Device for transdermal administration according to anyone of claims 1 - 5, characterized in that reboxetine essentially is in its S-isomeric form.

8. Device for transdermal administration according to anyone of claims 1 - 5, characterized in that reboxetine essentially is in racemic form.

9. Device for transdermal administration according to anyone of claims 1 - 8, characterized in that it is of the reservoir type, the matrix type, the drug-in-adhesive type, the multi-laminate type, the polymer-system with no foils type, and/or the iontophoretic type or combinations thereof, preferably of the drug-in-adhesive type or the reservoir type or combinations of these two types.

10. Device for transdermal administration according to anyone of claims 1 - 8, characterized in that it is of the electroporation, electroosmosis, electroincorporation or jet injection type.

11. Device for transdermal administration according to anyone of the preceding claims, characterized in that it has a loading of reboxetine providing for a daily dosage of from about 0.1 mg to about 20 mg.

20 12. Device for transdermal administration according to anyone of the preceding claims, characterized in that it delivers reboxetine for a predefined period of time, preferably 12, 24 or 48 hours, or up to 7 or 14 days.

13. Device according to anyone of the preceding claims, characterized in that reboxetine is present in a complex with cyclodextrin, preferably β -cyclodextrin.

25 14. Device according to anyone of the preceding claims, characterized in that it has a release profile being such that it, when applied on the skin at the appropriate time during day or night, administers reboxetine in such a way that a therapeutically effective systemic level of reboxetine prevails mainly during such periods of time during day and night when an antidepressant effect is most desirable.

30 15. Device according to anyone of the preceding claims, characterized in that it further comprises a substance enhancing transdermal penetration.

16. Device according to anyone of the preceding claims, characterized in that it further comprises a substance reducing irritant reactions.

17. Device according to anyone of the preceding claims, characterized in that it is occlusive.

18. Set of formulations of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s), characterized in that it comprises at least one device according to any one of the preceding claims and at least one formulation for oral, sublingual, buccal, nasal, pulmonary, rectal and/or other transmucosal administration.

19. Use of a compound comprising reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s), for the manufacture of a composition to be administered transdermally for achieving an antidepressant effect and/or an effect against symptoms associated with this condition.

20. Use of a compound comprising reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s), for the manufacture of a composition to be administered transdermally for treating addictive disorders and withdrawal syndromes, adjustment disorders, age-associated learning and mental disorders, anorexia nervosa, apathy, attention-deficit disorders due to general medical conditions, attention-deficit hyperactivity disorders, bipolar disorders, bulimia nervosa, chronic fatigue syndrome, conduct disorders, cyclothymic disorders, depression, dysthymic disorders, fibromyalgia and other somatoform disorders, stress incontinence, generalized anxiety disorders, inhalation disorders, an intoxication disorders, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorders, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, psychotic disorders, seasonal affective disorder, sleep disorder, social phobia, specific developmental disorders and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome or symptoms associated with said conditions.

21. Use of a compound comprising reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s), for the manufacture of a composition to be administered transdermally for achieving an anti-reserpine effect and/or a noradrenaline reuptake inhibiting effect.

22. Use according to anyone of claims 19 - 21, characterized in that reboxetine essentially is in its R-isomeric form.

23. Use according to anyone of claims 19 - 21, characterized in that reboxetine essentially is in its S-isomeric form.

24. Use according to anyone of claims 19 - 21, characterized in that reboxetine essentially is in racemic form.

5 25. Use according to anyone of claims 19 - 24, characterized in that the transdermal delivery is carried out using a device for transdermal delivery, such device especially being of the reservoir type, the matrix type, the drug-in-adhesive type, the multi-laminate type, the polymer-system with no foils type, and/or the iontophoretic type or combinations thereof, preferably of the drug-in-adhesive type or the reservoir
10 type or combinations of these two types.

26. Use according to anyone of claims 19 - 24, characterized in that the transdermal delivery is carried out using a device of the electroporation, electroosmosis, electroincorporation or jet injection type.

15 27. Use according to claim 25 or 26, characterized in that more than one transdermal device is used at a time.

28. Method for achieving an antidepressant effect in a living body or for achieving an effect when treating addictive disorders and withdrawal syndromes, adjustment disorders, age-associated learning and mental disorders, anorexia nervosa, apathy, attention-deficit disorders due to general medical conditions, attention-deficit
20 hyperactivity disorders, bipolar disorders, bulimia nervosa, chronic fatigue syndrome, conduct disorders, cyclothymic disorders, depression, dysthymic disorders, fibromyalgia and other somatoform disorders, stress incontinence, generalized anxiety disorders, inhalation disorders, an intoxication disorders, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorders, panic disorder, peripheral
25 neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, psychotic disorders, seasonal affective disorder, sleep disorder, social phobia, specific developmental disorders and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome, or for achieving an anti-reserpine and/or noradrenaline reuptake inhibiting effect, by transdermal administration of a compound comprising reboxetine, optionally
30 encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s).

29. Method according to claim 28, characterized in that reboxetine essentially is in its R-isomeric form.

30. Method according to claim 28, characterized in that reboxetine essentially is in its S-isomeric form.

31. Method according to claim 28, characterized in that reboxetine essentially is in racemic form.

5 32. Method according to anyone of claims 28 -31 wherein the treatment is achieved through systemic effect of the transdermally administered compound.

33. Method according to anyone of claims 28- 32 wherein the transdermal administration is carried out using a device for transdermal delivery, such device especially being of the reservoir type, the matrix type, the drug-in-adhesive type, the multi-laminate type, the polymer-system with no foils type, and/or the iontophoretic type or combinations thereof, preferably of the drug-in-adhesive type or the reservoir type or combinations of these two types.

34. Method according to anyone of claims 28- 32 wherein the transdermal administration is carried out using a device for transdermal delivery device of the electroporation, electroosmosis, electroincorporation or jet injection type.

35. Method according to anyone of claims 28 - 34 wherein more than one device for transdermal delivery is used at a time.

36. Method for achieving an antidepressant effect and/or symptoms associated with this condition in a living body or for achieving an effect when treating addictive disorders and withdrawal syndromes, adjustment disorders, age-associated learning and mental disorders, anorexia nervosa, apathy, attention-deficit disorders due to general medical conditions, attention-deficit hyperactivity disorders, bipolar disorders, bulimia nervosa, chronic fatigue syndrome, conduct disorders, cyclothymic disorders, depression, dysthymic disorders, fibromyalgia and other somatoform disorders, stress incontinence, generalized anxiety disorders, inhalation disorders, an intoxication disorders, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorders, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, psychotic disorders, seasonal affective disorder, sleep disorder, social phobia, specific developmental disorders and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome, or for achieving an anti-reserpine and/or noradrenaline reuptake inhibiting effect, by transdermal administration of a compound comprising reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s) in combination with oral, sublingual, buccal, nasal, pulmonary, rectal and/or other transmucosal administra-

tion of a compound comprising reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s).

37. Method according to anyone of the claims 28 - 36, **characterized** in that reboxetine is administered in such a way that a therapeutically effective systemic level of reboxetine prevails mainly during those periods of time during day and night when an effect is most desirable.

38. Method according to anyone of the claims 28 - 36, **characterized** in that reboxetine is administered in such a way that a less than therapeutically effective systemic level of reboxetine prevails mainly during those periods of time during day and night when an antidepressant effect is less desirable.

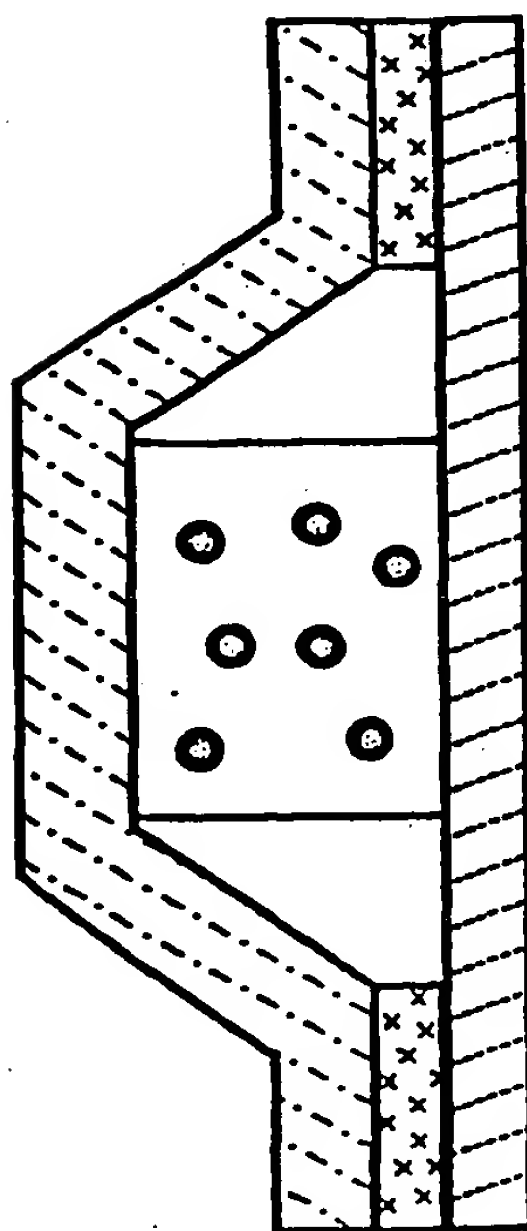


Fig. 1 A Matrix

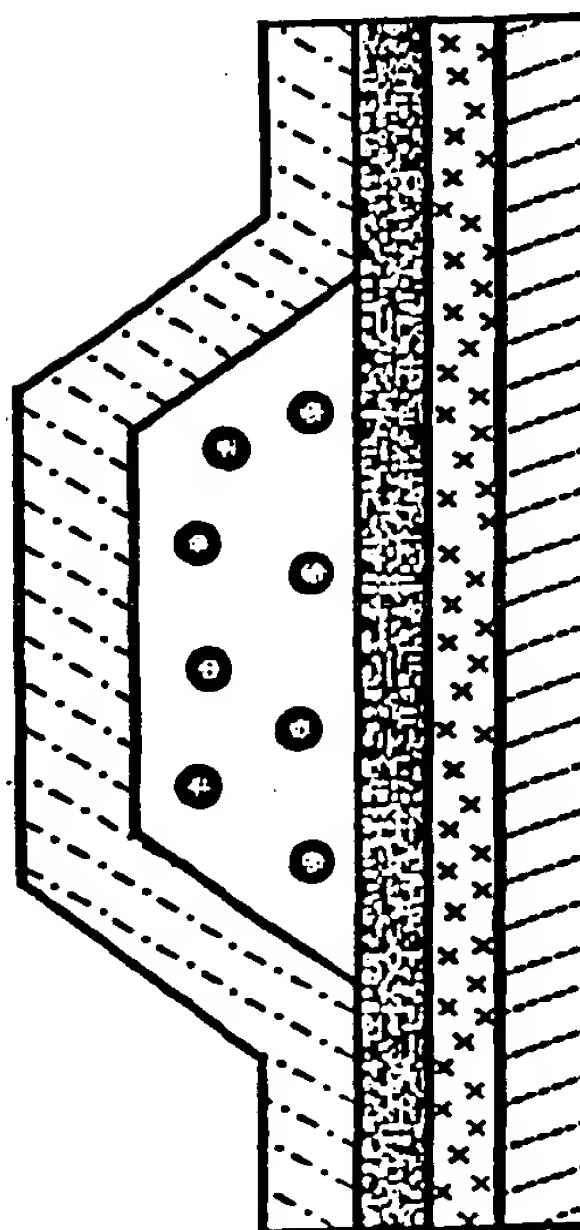


Fig. 1 C Reservoir

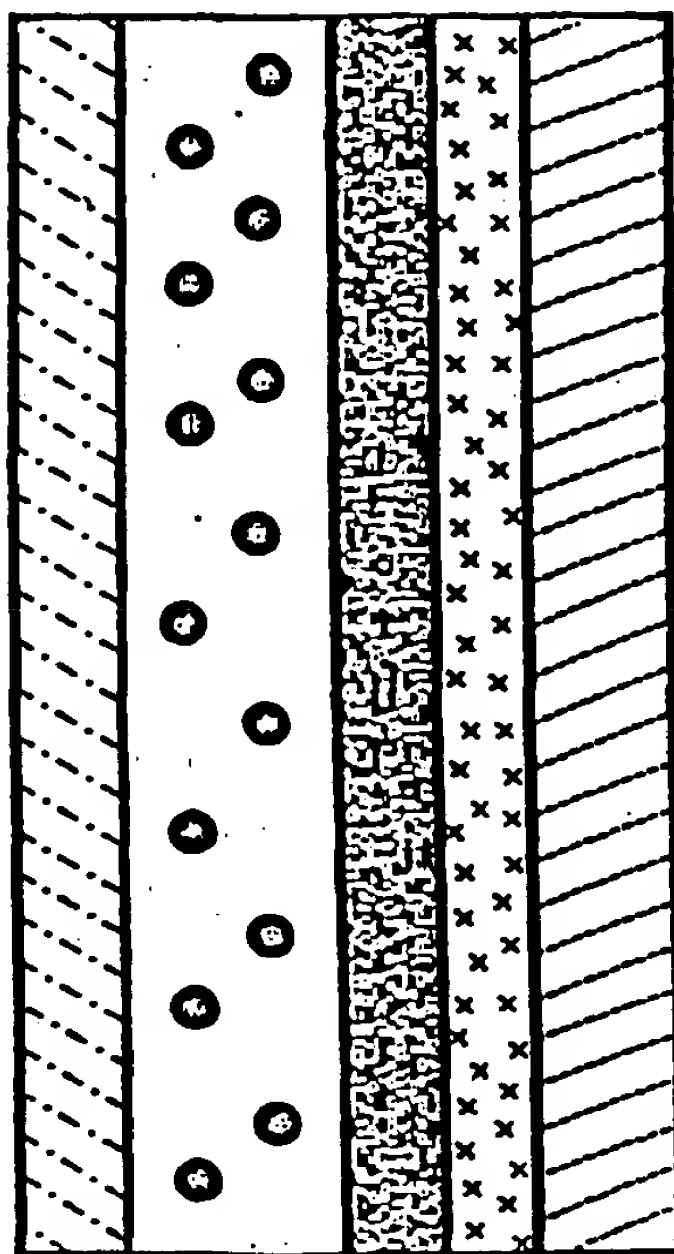


Fig. 1 B Multi-laminate

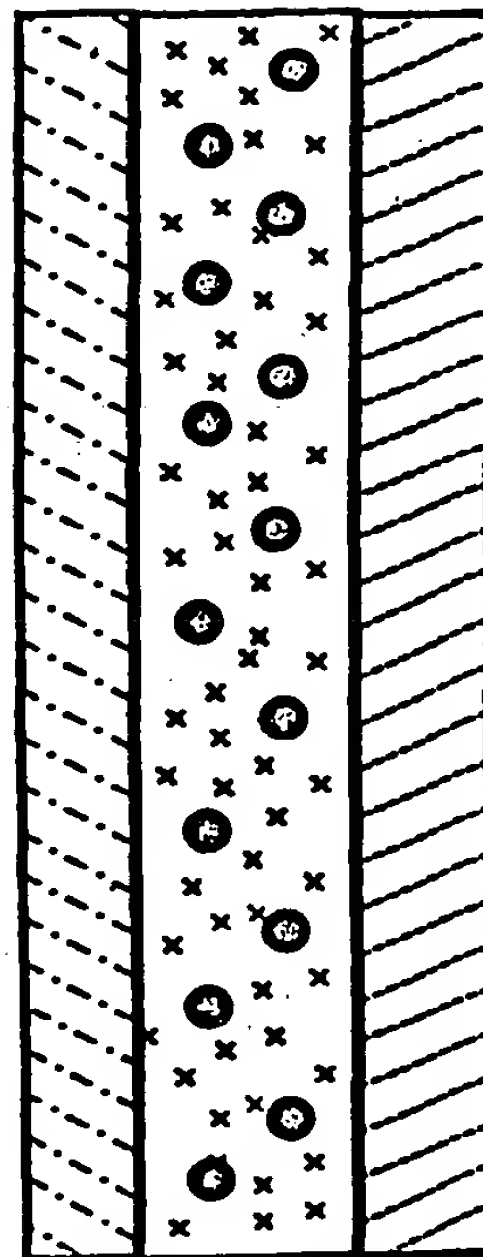
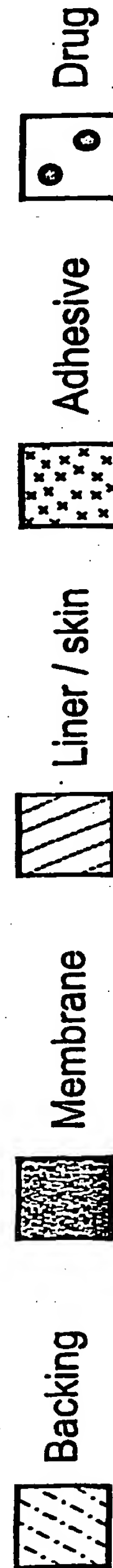


Fig. 1 D Drug-in-adhesive



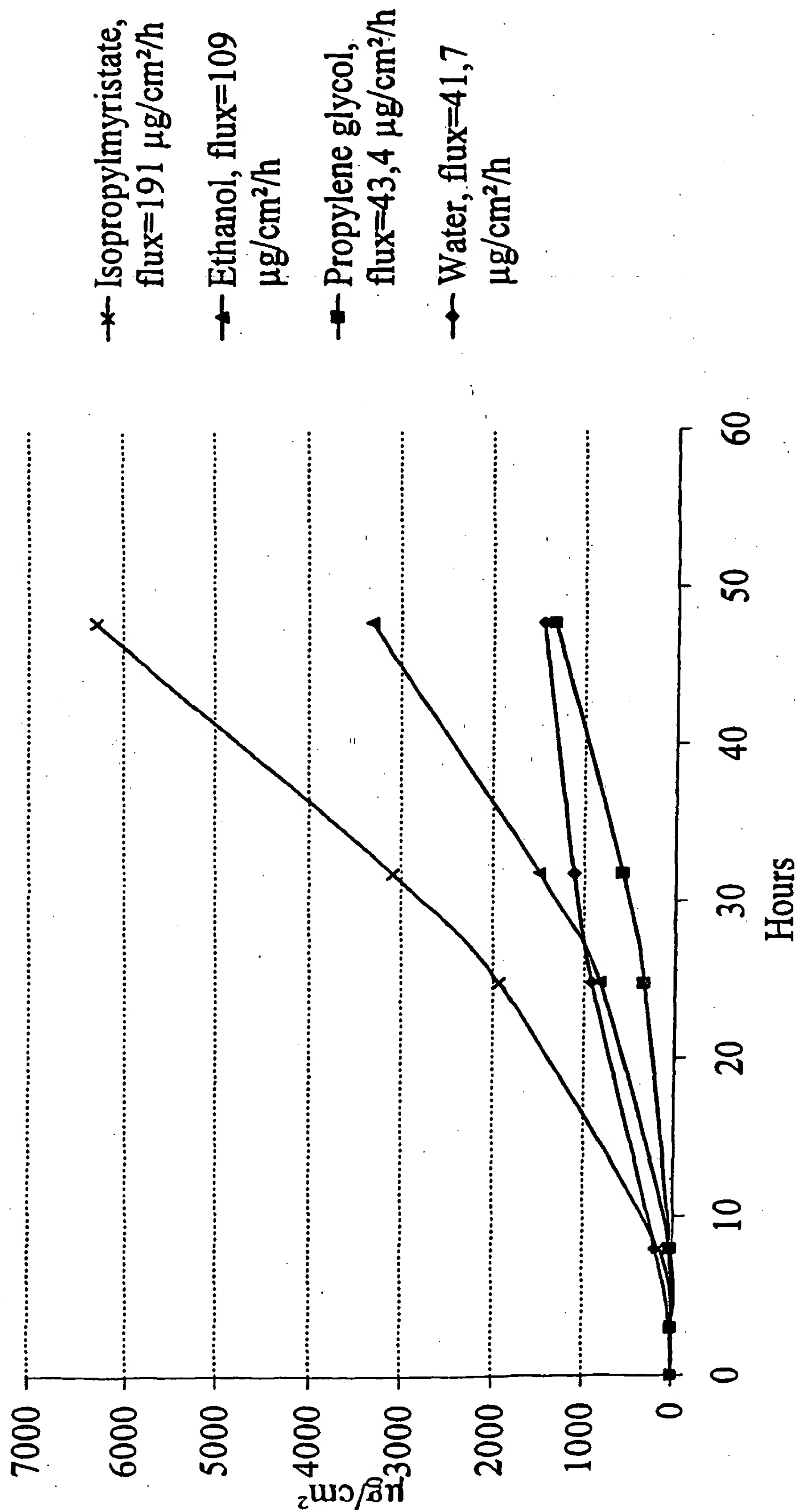


Figure 2

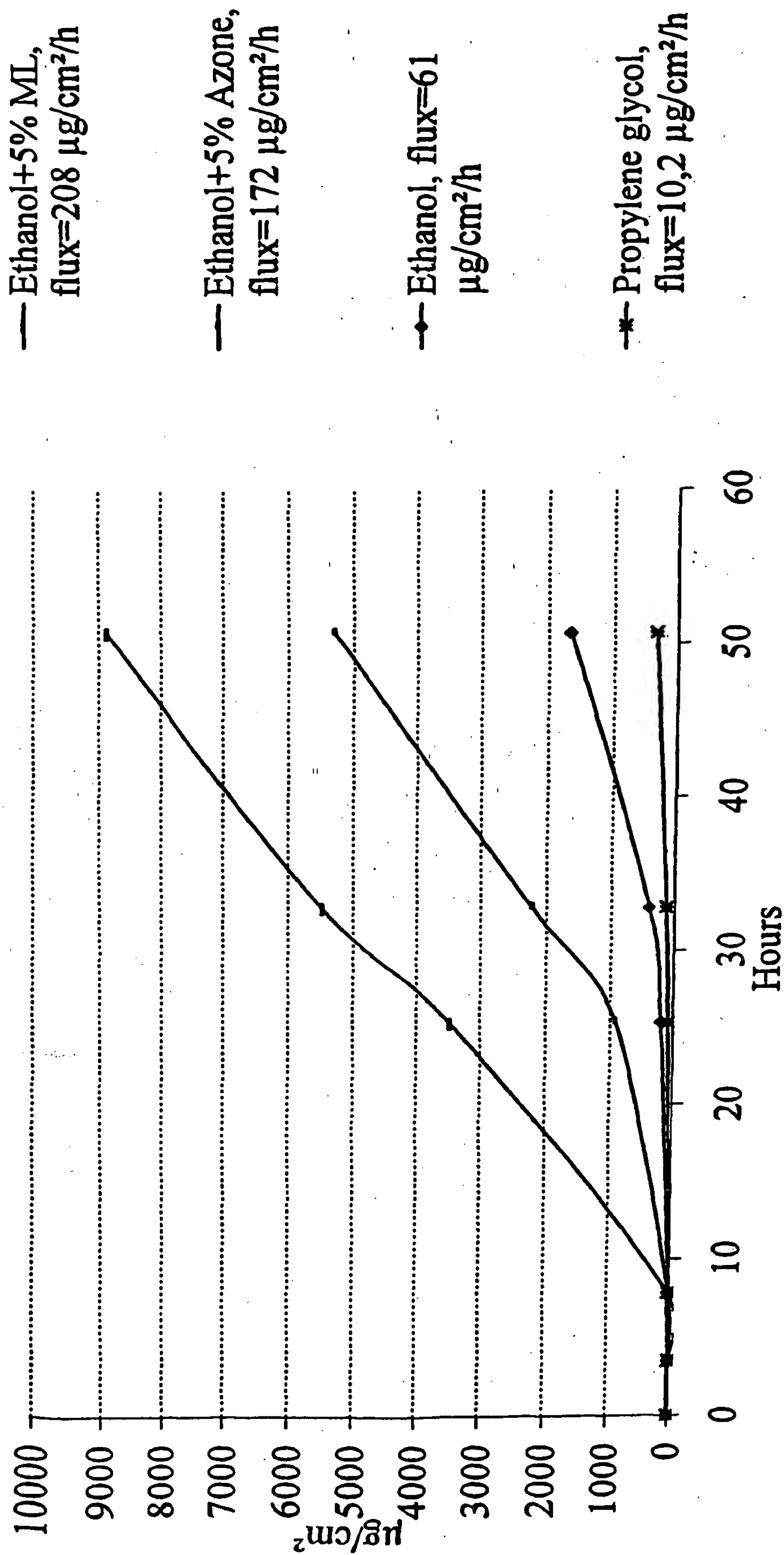


Figure 3

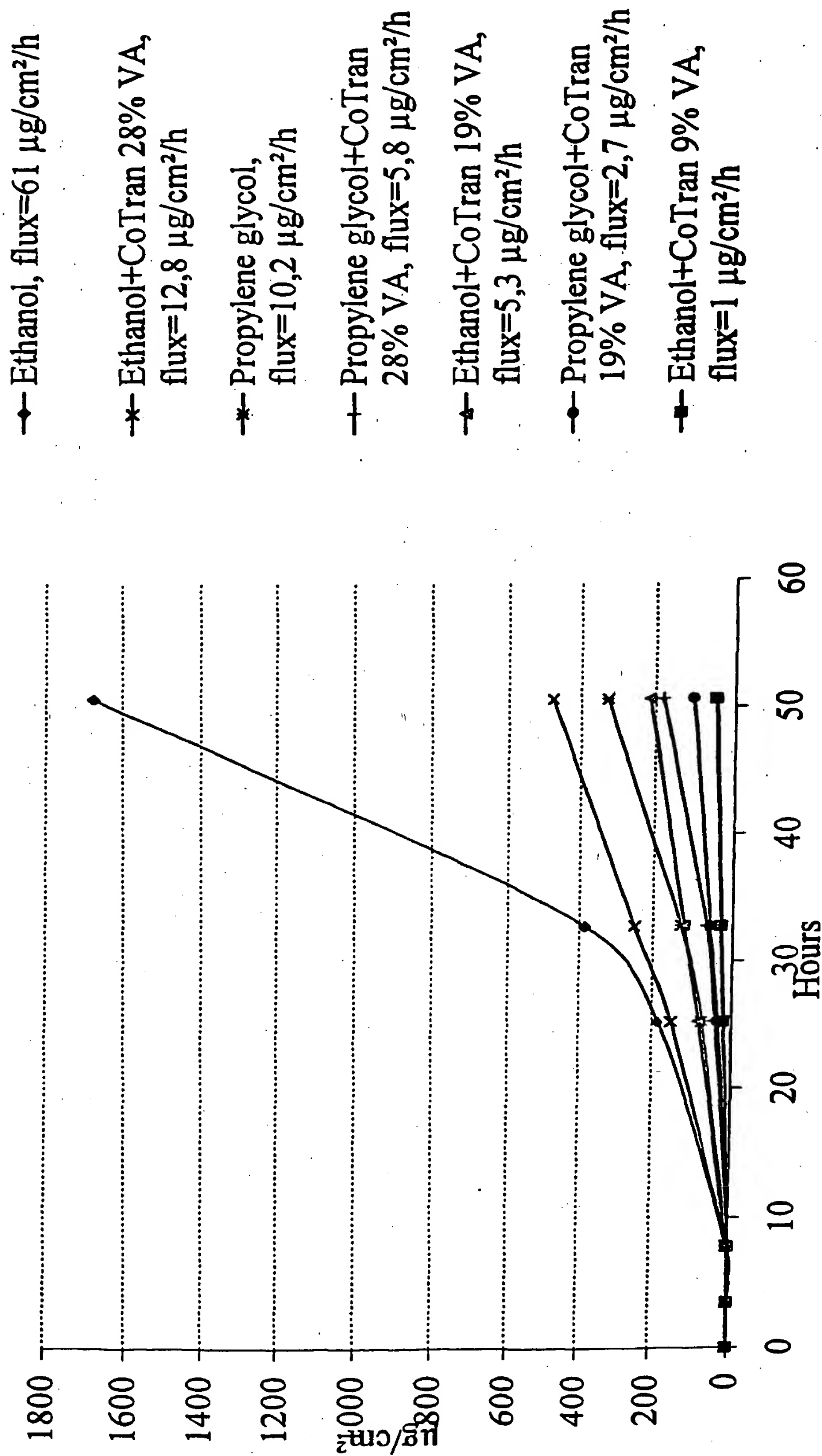


Figure 4

5/14

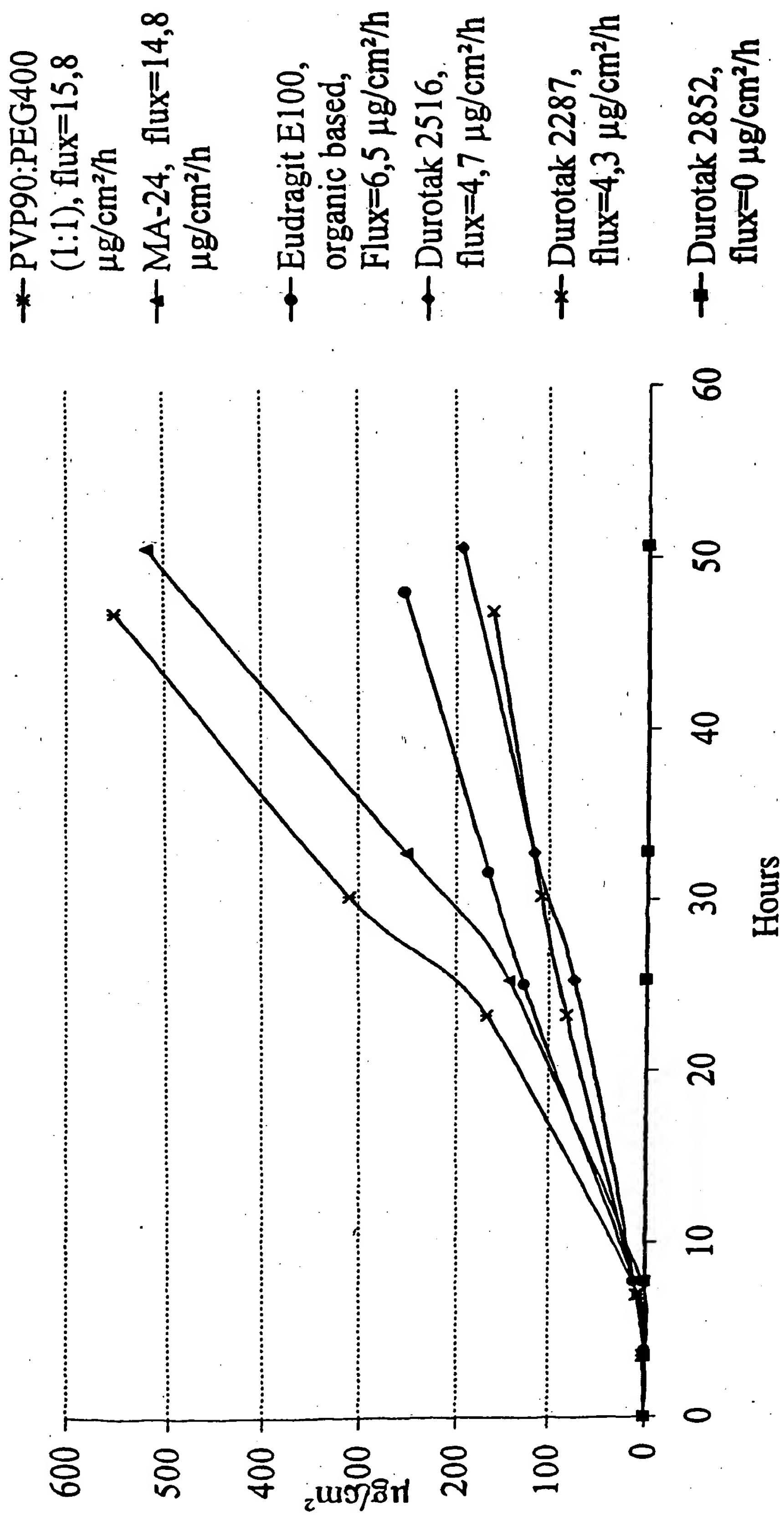


Figure 5

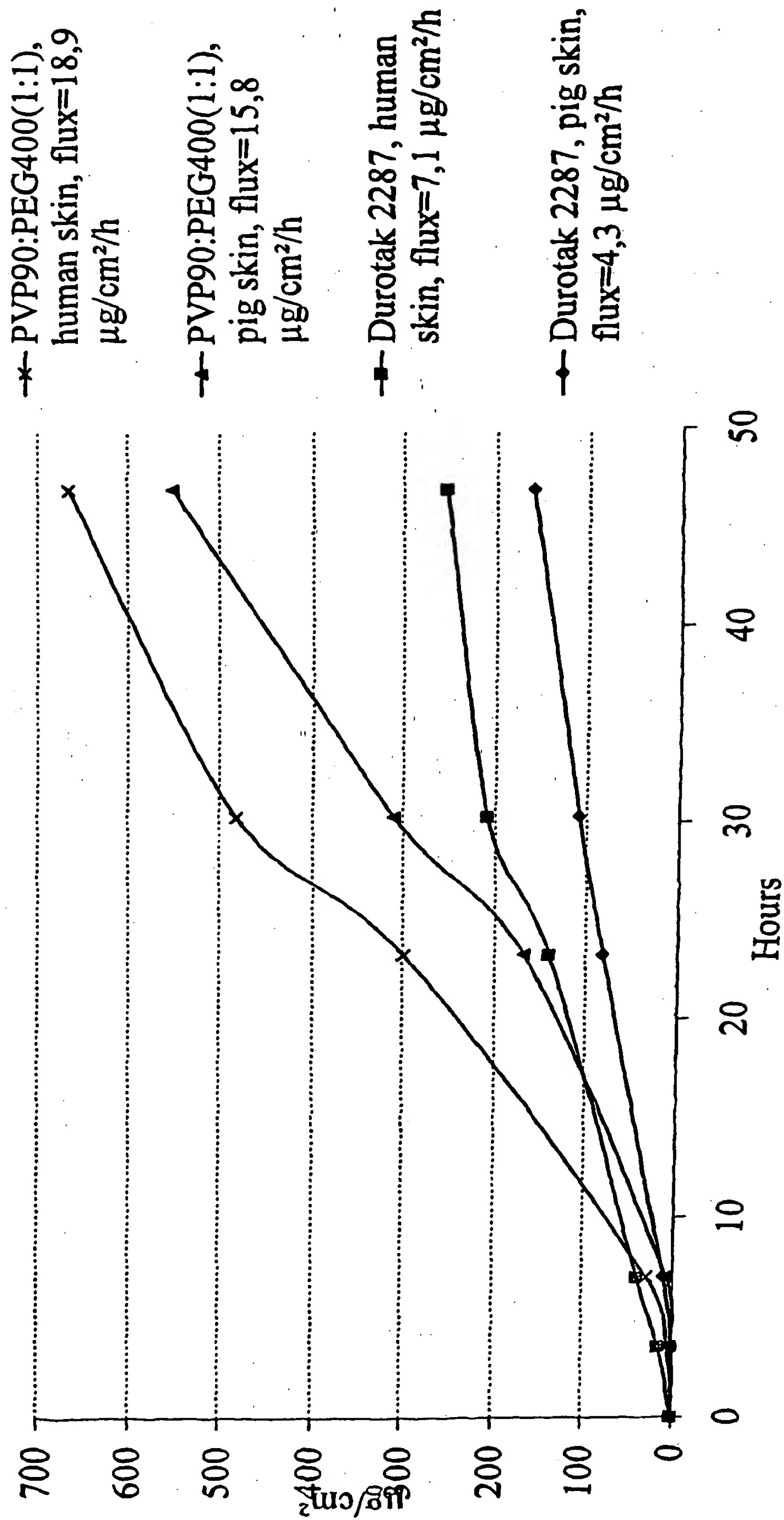


Figure 6

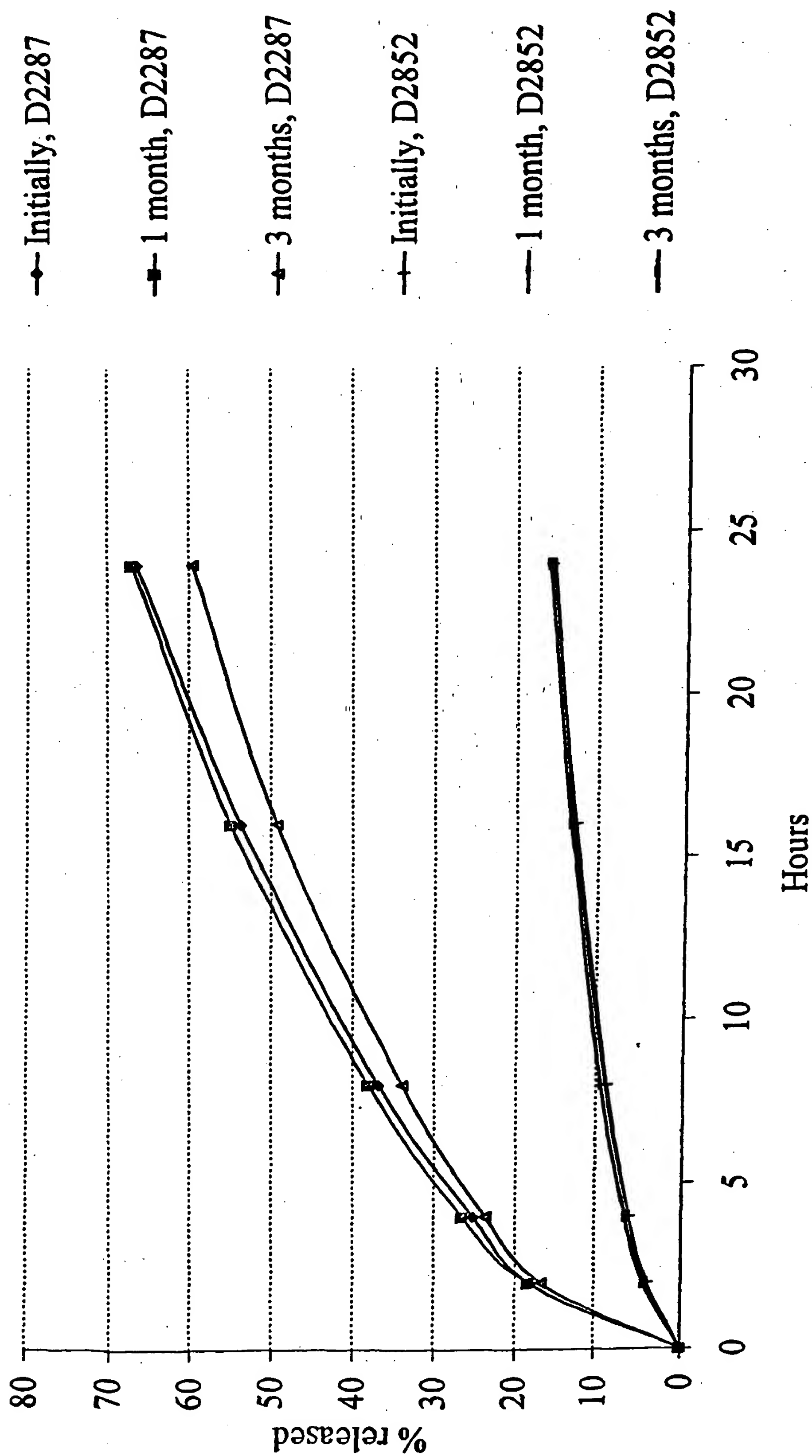


Figure 7

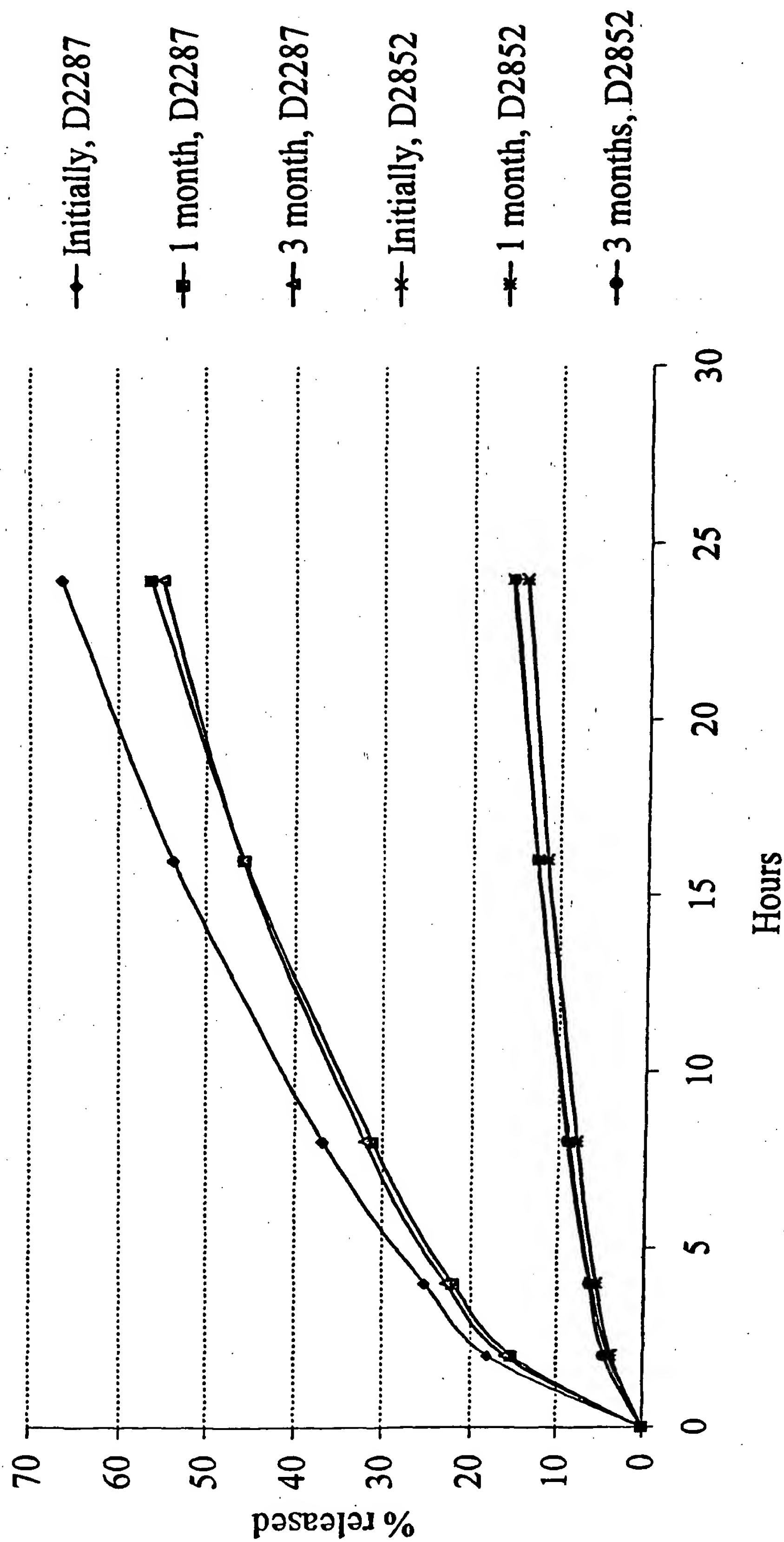


Figure 8

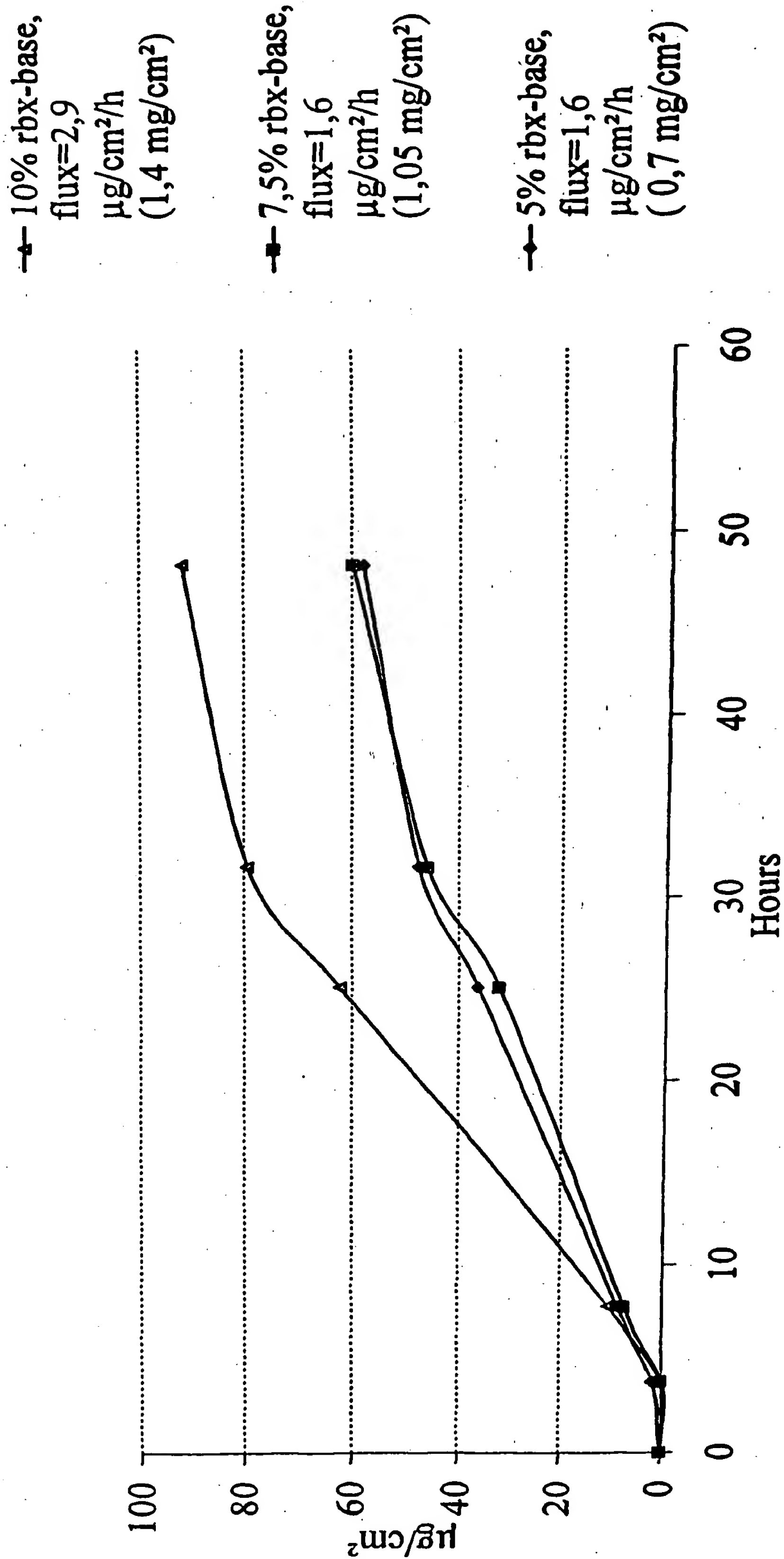


Figure 9

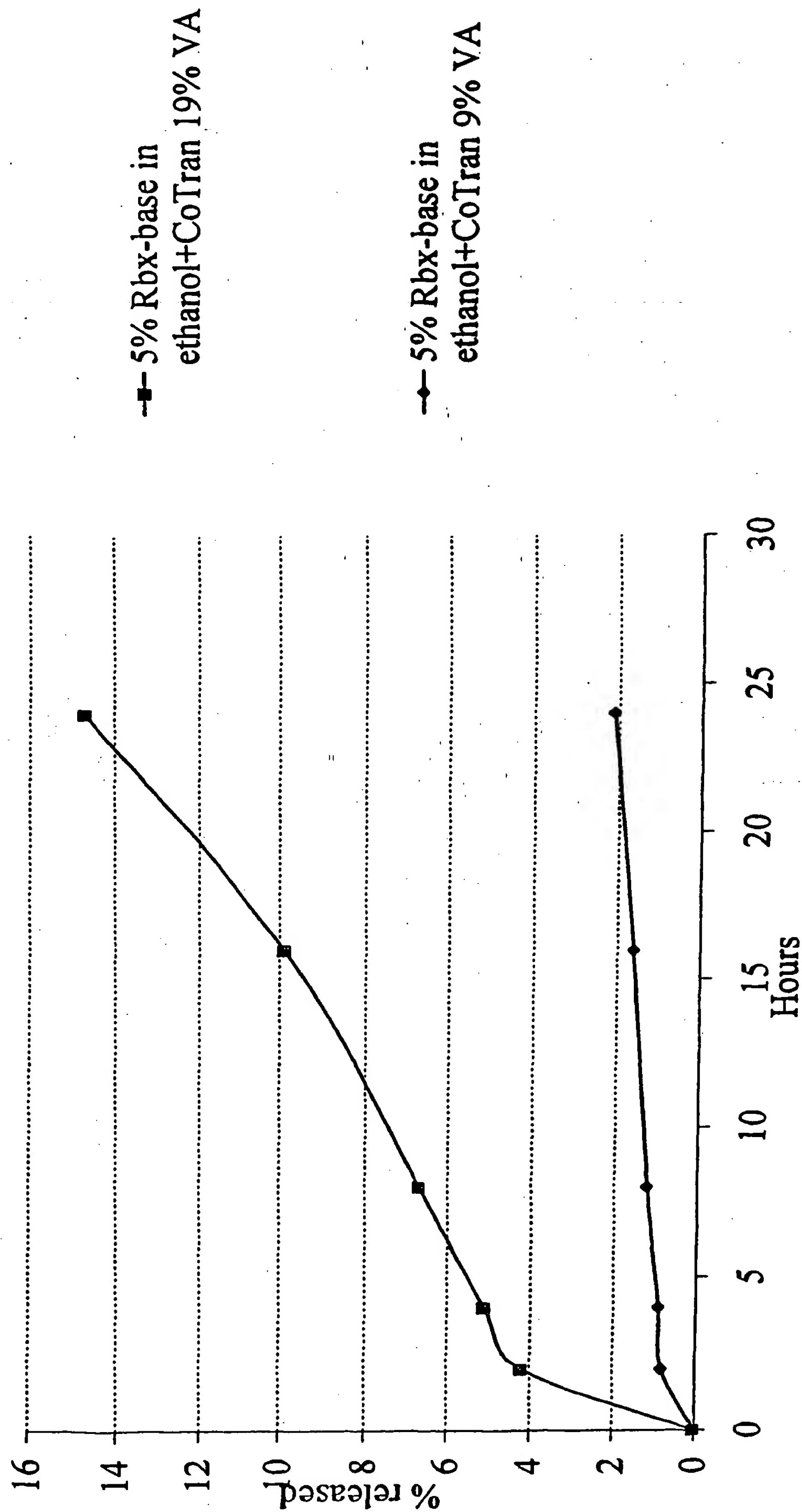


Figure 10

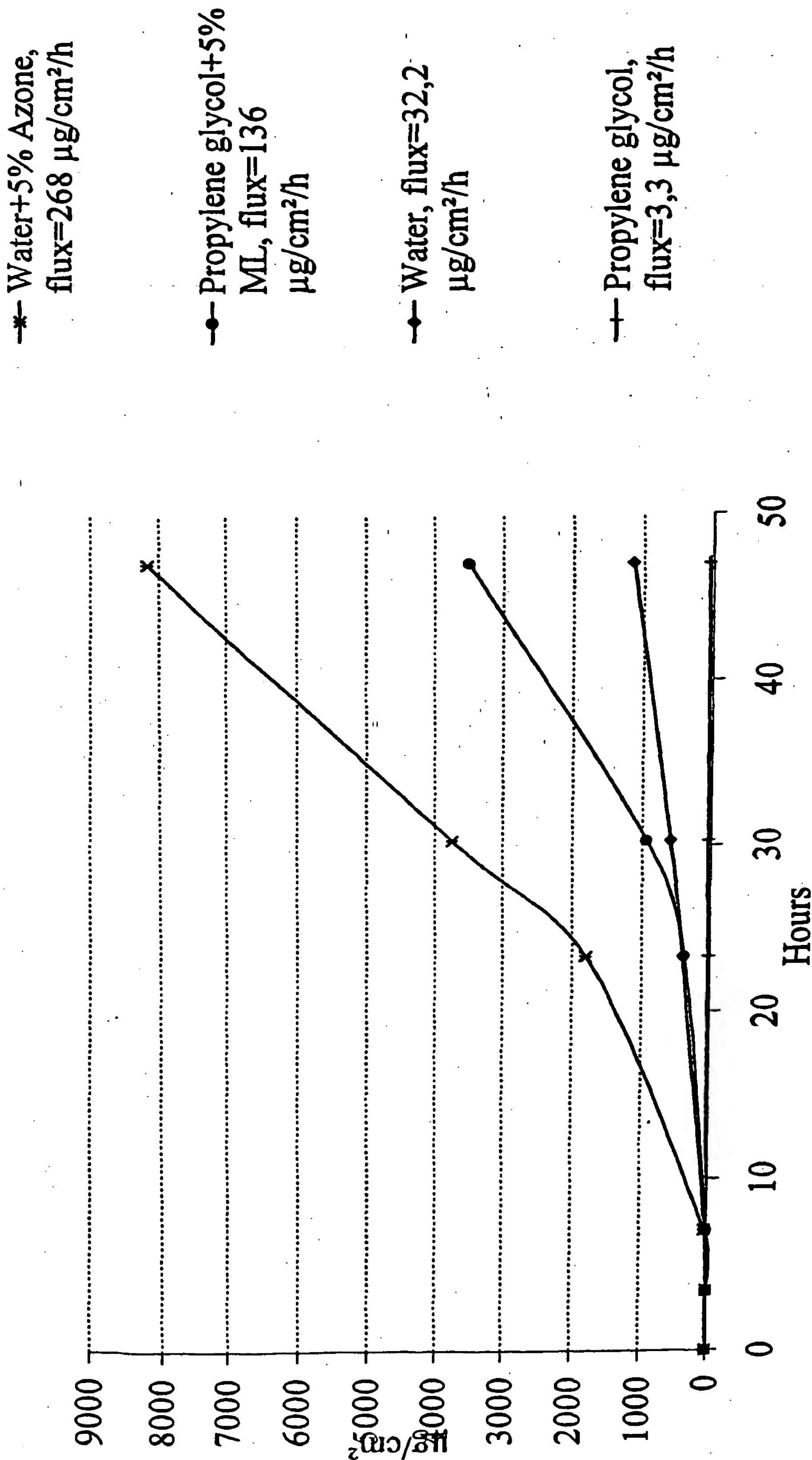


Figure 11

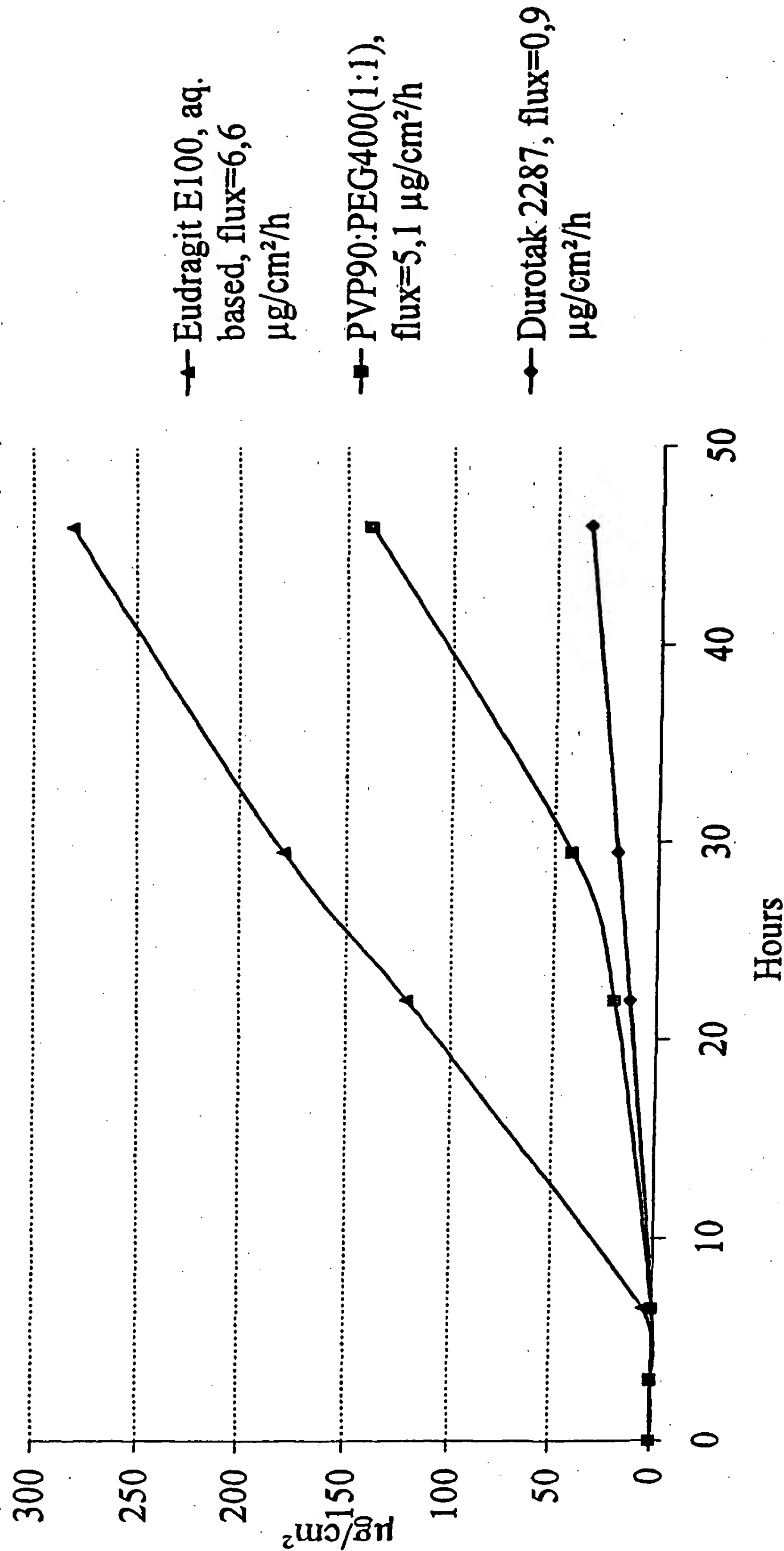


Figure 12

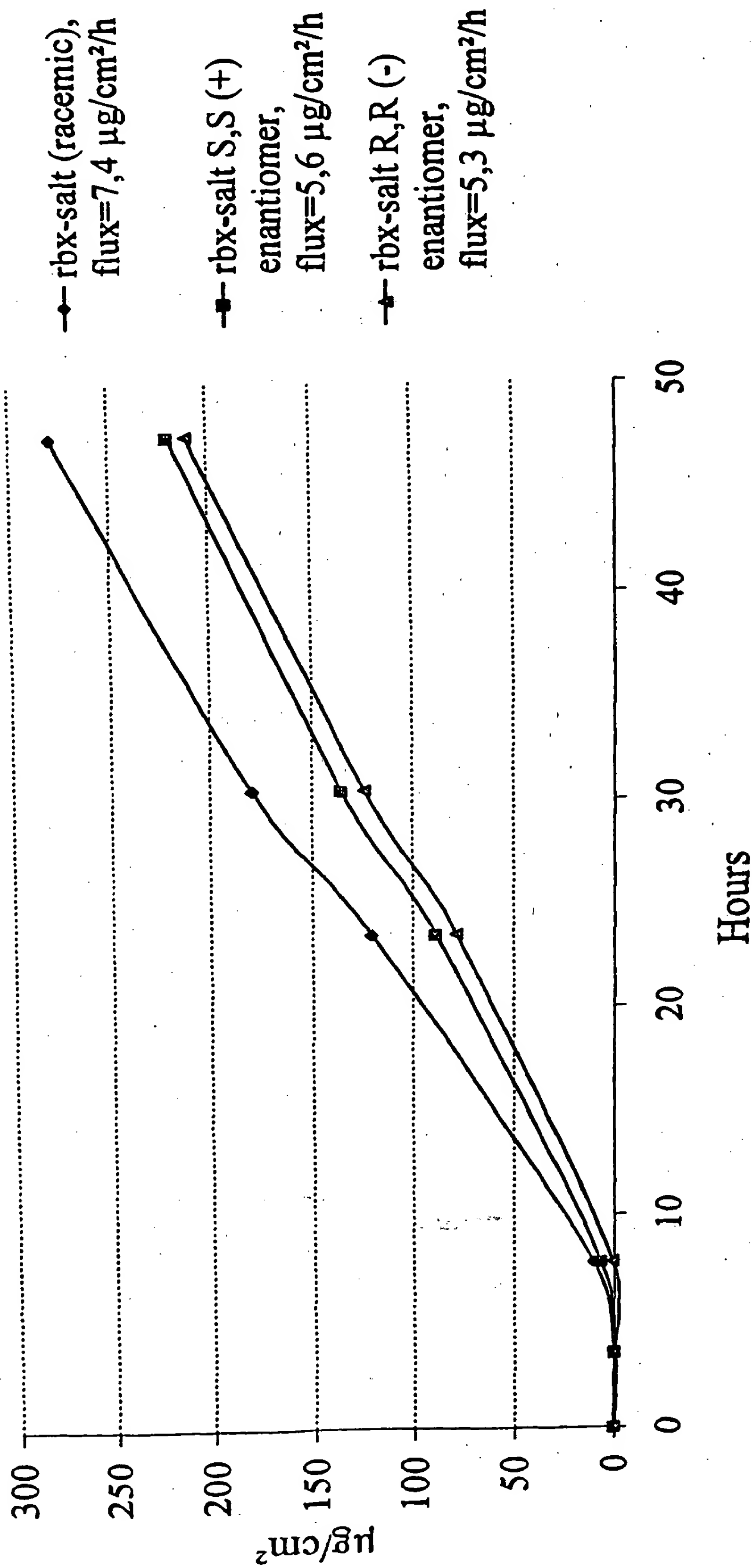


Figure 13

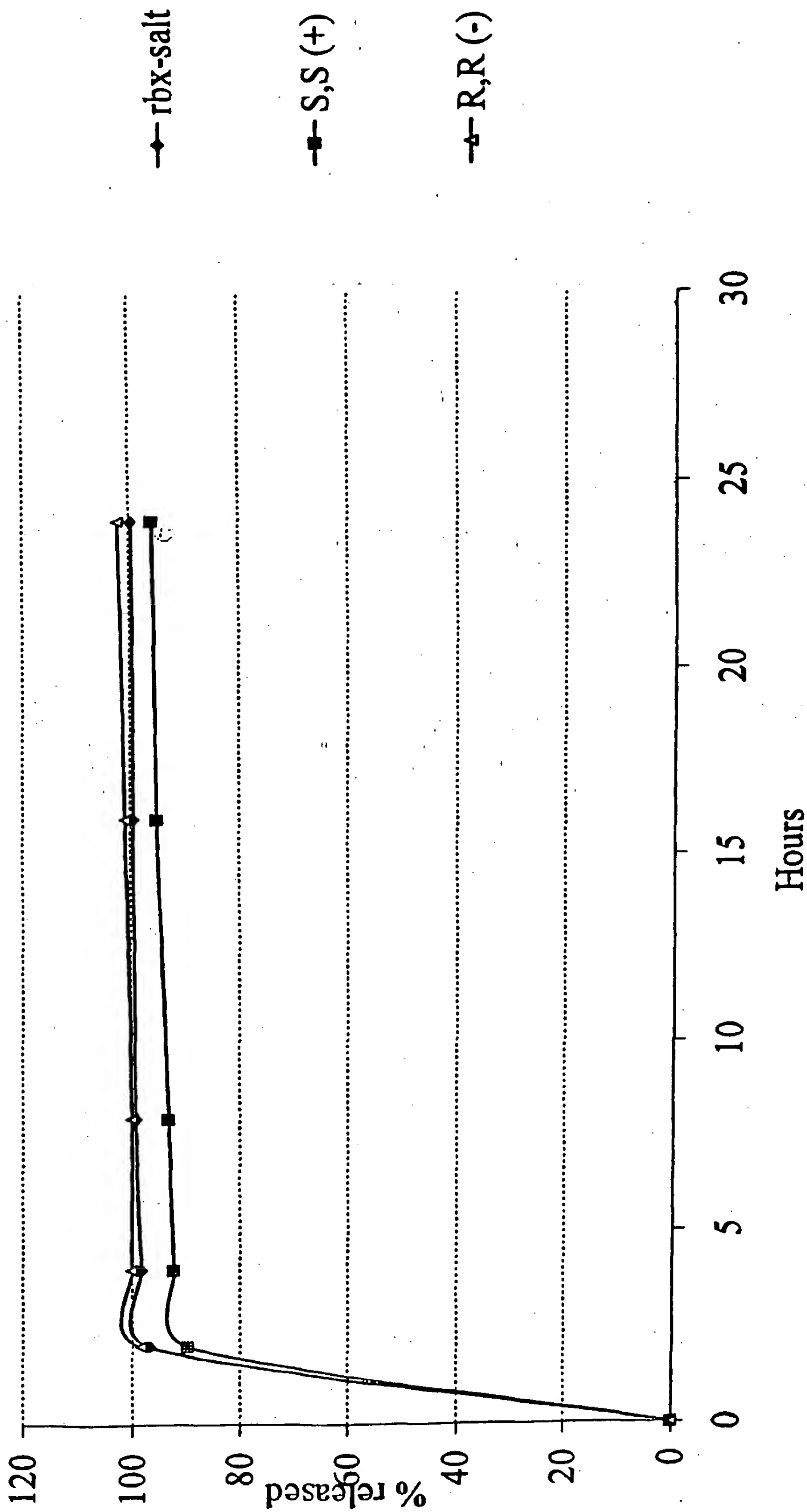


Figure 14

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/70, A61K 31/5375, A61P 25/24
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9911208 A1 (WILLIAMS, C., DONALD), 11 March 1999 (11.03.99), see claim 32 and example 34 --	1-38
A	ADHESIVES AGE, September 1995, Steven M. Wick: "Developing A Drug-In-Adhesive Design For Transdermal Drug Delivery", page 18 - page 24 --	1-38
A	ADIS DRUG EVALUATION, Volume 12, No 1, July 1999, Kristin J. Holm et al, "Reboxetine. A Review of its Use in Depression" page 65 - page 83 -- -----	1-38

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 January 2001

Date of mailing of the international search report

29 -01- 2001

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01972

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 28-38
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01972

Claims 28-38 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/12/00

International application No.

PCT/SE 00/01972

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9911208 A1	11/03/99	AU 5155198 A	22/03/99

Form PCT/ISA/210 (patent family annex) (July 1998)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
30 August 2001 (30.08.2001)

PCT

(10) International Publication Number
WO 01/62236 A2

(51) International Patent Classification⁷: A61K 31/00

(21) International Application Number: PCT/US01/03698

(22) International Filing Date: 23 January 2001 (23.01.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/184,790 24 February 2000 (24.02.2000) US

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(54) Title: NEW DRUG COMBINATIONS

(57) Abstract: A composition comprising: (a) a pharmaceutically effective amount of one or more norepinephrine reuptake inhibitors or a pharmaceutically effective salt thereof; and (b) a pharmaceutically effective amount of one or more antimuscarinic agents or a pharmaceutically effective salt thereof is provided. The composition is useful in treating disorders or diseases of the central nervous system, and particularly useful in treating incontinence.

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NEW DRUG COMBINATIONS

Background of the Invention

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1. Field of the Invention

This invention describes new treatments that should provide for a fast acting rapid onset of relief from several nervous system disorders, and it involves the
10 administration of a norepinephrine reuptake inhibitor, preferably a selective norepinephrine reuptake inhibitor, most preferably the drug reboxetine, in combination with an antimuscarinic agent, preferably tolterodine. In particular, the combination is to be used to treat incontinence.

15 2. Technology Description

The introduction of tricyclic antidepressants in the early 1960s has provided a major advance in the treatment of neuropsychiatric disorders. Reactive and endogenous
20 depressions, diagnoses formerly carrying grave prognostic implications, have become, with the introduction of the tricyclics, manageable disorders with a much smaller toll on the patient and the society as a whole.

The early tricyclic compounds were reuptake inhibitors of all the catecholamines released in the synaptic cleft, thus resulting in prolongation and enhancement of the
25 dopamine (DA), noradrenaline (NA) and serotonin (5-hydroxytryptamine = 5-HT) action. Lack of selectivity also causes undesired side effects particularly on the acetylcholine (especially the muscarinic component), and histamine mediated neurotransmission.

30 Because of these unwanted pharmacodynamic activities, cognitive impairment, sedation, urinary and gastrointestinal tract disturbances, and increased intraocular pressure were limiting factors in the clinical use of these compounds and often

required discontinuation of treatment. Of utmost concern were also the cardiac toxic effects and the proconvulsant activity of this group of drugs.

More recently, selective reuptake inhibitors for serotonin (SSRI) have been introduced
5 with definite advantages in regard to fewer side effects without loss of efficacy. Fluoxetine is an example of such an inhibitor that has had a great amount of commercial success.

Another class of compounds that has been proposed for use in the treatment of
10 depression is selective norepinephrine reuptake inhibitors. Lower-than-normal levels of norepinephrine are associated with a variety of symptoms including lack of energy, motivation, and interest in life. Thus, a normal level of norepinephrine is essential to maintaining drive and capacity for reward. These neurotransmitters travel from the
15 terminal of a neuron across a small gap (*i.e.*, the synaptic cleft) and bind to receptor molecules on the surface of a second neuron. This binding elicits intracellular changes that initiate or activate a response or change in the postsynaptic neuron. Inactivation occurs primarily by transport (*i.e.*, reuptake) of the neurotransmitter back into the presynaptic neuron. Abnormality in noradrenergic transmission results in
20 various types of depression, mental, behavioral, and neurological disorders attributed to a variety of symptoms including a lack of energy, motivation, and interest in life. *See generally*, R.J. Baldessarini, "Drugs and the Treatment of Psychiatric Disorders: Depression and Mania" in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, McGraw-Hill, NY, NY, pp. 432-439 (1996).

25 Examples of norepinephrine reuptake inhibitors (both selective and not selective) include, but are not limited to the following: tandamine (CAS 42408-80-0; US 3904617; US 4118394), pirandamine (CAS 42408-79-7; US 3995052), ciclazindol (CAS 37751-39-6; US 3891644; US 3957819; US 3976645), fluparoxan (US 4880801), lortalamine (CAS 70384-91-7; US 4201783), talsupram (CAS 21489-20-
30 3), talopram (CAS 7182-51-6), prindamine, nomifensine (US 3577424), viloxazine (US 3712890), tomoxetine (US 4314081), duloxetine (US 5023269), venlafaxine (US 4535186), milnacipran (US 4478836) and reboxetine (US 4229449).

Tomoxetine, (R)-(-)-N-methyl-3-(2-methylphenoxy)-3-phenylpropylamine is disclosed in U.S. Patent No. 4,314,081. Reboxetine, 2-[alpha-(2-ethoxy)phenoxybenzyl]morpholine is disclosed in U.S. Patent No. 4,229,449. Reboxetine includes both the racemate, as well as the (-)(R,R) and (+)(S,S) enantiomers. This product is also identified by the following trademarks: VESTRA, PROLIFT, NOREBOX and ERDONAX. Duloxetine, N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine is disclosed in U.S. Patent No. 4,956,388. It is usually administered as the hydrochloride salt and as the (+) enantiomer. Venlafaxine is identified as Compound A of U.S. Patent No. 4,761,501. Milnacipran, N,N-diethyl-2-aminomethyl-1-phenylcyclopropanecarboxamide is disclosed in U.S. Patent No. 4,478,836. To the extent necessary for completion, these above-cited documents are expressly incorporated by reference.

Antimuscarinic agents can be used to treat urinary incontinence. Examples of antimuscarinic agents include, but are not limited to the following: tolterodine, propiverine, oxybutynin, trospium, darifenacin, temiverine, ipratropium.

Tolterodine, Phenol, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methyl-, (R)-, an antimuscarinic with a high degree of bladder selectivity, has been developed and launched by Pharmacia & Upjohn under the DETROL® trademark for the treatment of incontinence associated with an overactive bladder. This product is disclosed in U.S. Patent No. 5,382,600. The active metabolites of tolterodine are

Propiverine is 1-methyl-4-piperidyl .alpha.,.alpha.-diphenyl-.alpha.-(n-propoxy)acetate and is disclosed in East German Patent No. 106643 and in CAS 82-155841s (1975). Oxybutynin is 4-(Diethylamino)-2-butynylalpha-phenylcyclohexaneglycolate and is disclosed in UK Patent No. 940540. Trospium is 3alpha-Hydroxyspiro[1alphaH,5alphaH-nortropane-8,1'-pyrrolidinium]chloride benzilate and is disclosed in U.S. Patent No. 3480623. Darifenacin is 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-alpha, alpha-diphenyl-, and is disclosed in U.S. Patent No. 5,096,890. Temiverine is Benzeneacetic acid, .alpha.-cyclohexyl-.alpha.-hydroxy-, 4-(diethylamino)-1,1-dimethyl-2-butynyl ester

and is disclosed in U.S. Patent No. 5036098 and ipratropium is 8-isopropylnoratropine methobromide and disclosed in U.S. Patent No. 3505337.

Despite the above advances in the art, it would be desirable to develop a
5 pharmaceutical composition that would have both the benefits of the norepinephrine reuptake inhibitors and that of the antimuscarinic agents.

Brief Summary of the Invention

10 In accordance with the present invention a novel pharmaceutical composition is provided. More specifically, the composition combines one or more selective norepinephrine reuptake inhibitors with one or more antimuscarinic agents, preferably tolterodine. The composition is considered to be particularly effective against
incontinence in general, and more particularly stress incontinence.

15

A first embodiment of the present invention provides a composition comprising:

(a) a pharmaceutically effective amount of one or more norepinephrine reuptake inhibitors or a pharmaceutically effective salt thereof; and

20

(b) a pharmaceutically effective amount of one or more antimuscarinic agents or a pharmaceutically effective salt thereof.

In particularly preferred embodiments, component (a) comprises reboxetine in either its
25 enantiomeric or racemic form and component (b) comprises tolterodine, including its active metabolites.

Yet another embodiment of the present invention provides a method for treating or preventing incontinence or diseases or disorders of the central nervous system
30 comprising administering a therapeutically effective amount of the above composition to a mammal. In most instances, the mammal will be a human, and the disease or disorder to be treated is incontinence.

A further embodiment of the present invention comprises the use of the above composition to prepare a medicament for treating or preventing incontinence or diseases or disorders of the central nervous system.

- 5 An object of the present invention is to provide novel compositions having biological activity.

A further object of the present invention is to provide a method for treating or preventing incontinence or diseases of the central nervous system by using the novel
10 compositions of the present invention.

An additional object of the present invention is to provide an effective treatment for incontinence.

- 15 These, and other objects, will readily be apparent to those skilled in the art as reference is made to the detailed description of the preferred embodiment.

Detailed Description of the Preferred Embodiment

- 20 In describing the preferred embodiment, certain terminology will be utilized for the sake of clarity. Such terminology is intended to encompass the recited embodiment, as well as all technical equivalents which operate in a similar manner for a similar purpose to achieve a similar result. To the extent that any pharmaceutically active compound is disclosed or claimed, it is expressly intended to include all active metabolites produced
25 *in vivo*, and, is expressly intended to include all enantiomers, isomers or tautomers where the compound is capable of being present in its enantiomeric, isomeric or tautomeric form.

- The present invention provides a novel composition which is a combination of different
30 chemical entities, more specifically, the first entity being a norepinephrine reuptake inhibitor and the second being an antimuscarinic agent.

The first component is a norepinephrine reuptake inhibitor, with selective norepinephrine reuptake inhibitors being particularly preferred. This list of compounds includes, but is not limited to the following: tandamine, pirandamine, ciclazindol, fluparoxan, lortalamine, talsupram, talopram, prindamine, nomifensine, viloxazine, tomoxetine, duloxetine, venlafaxine, milnacipran and reboxetine, with reboxetine being particularly preferred.

Examples of pharmaceutically effective salts for the selective norepinephrine reuptake inhibitor include, but are not limited to salts prepared from pharmaceutically acceptable acids or bases, including organic and inorganic acids and bases. When the preferred compound of use is basic (for example reboxetine), salts may be prepared from pharmaceutically acceptable acids. Suitable pharmaceutically acceptable acids include acetic, benzenesulfonic (besylate), benzoic, p-bromophenylsulfonic, camphorsulfonic, carbonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, hydroiodic, isethionic, lactic, maleic, malic, mandelic, methanesulfonic (mesylate), mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, and the like. Examples of such pharmaceutically acceptable salts include, but are not limited to, acetate, benzoate, hydroxybutyrate, bisulfate, bisulfite, bromide, butyne-1,4-dioate, carpoate, chloride, chlorobenzoate, citrate, dihydrogenphosphate, dinitrobenzoate, fumarate, glycollate, heptanoate, hexyne-1,6-dioate, hydroxybenzoate, iodide, lactate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, oxalate, phenylbutyrate, phenylproionate, phosphate, phthalate, phylacetate, propanesulfonate, propiolate, propionate, pyrophosphate, pyrosulfate, sebacate, suberate, succinate, sulfate, sulfite, sulfonate, tartrate, xylenesulfonate, and the like.

In particularly preferred embodiments the selective norepinephrine reuptake inhibitor is reboxetine, 2-[α -((2-ethoxyphenoxy)benzyl)]-morpholine, and its pharmaceutically acceptable salts, in either its enantiomeric (particularly the (S,S) enantiomer) or racemic form. Synthesis of racemic reboxetine is described in greater detail in U.S. Patent No. 4,229,449. Individual stereoisomers of reboxetine can be obtained by resolution of the racemic mixture of enantiomers using conventional methods

generally known by those skilled in the art. Such methods include, but are not limited to, resolution by simple crystallization and chromatographic techniques, for example, as set forth in GB 2,167,407. Other methods of preparation are described in US 5,068,433 and US 5,391,735. Reboxetine can be a free base form, or it can be in salt form, preferably the methanesulfonate salt (also called reboxetine mesylate). To the extent necessary for completion, the above patents are expressly incorporated by reference.

The selection of the dosage of the first component is that which can provide relief to the patient. As is well known, the dosage of this component depends on several factors such as the potency of the selected specific compound, the mode of administration, the age and weight of the patient, the severity of the condition to be treated, and the like. This is considered to be within the skill of the artisan and one can review the existing literature on the components to determine optimal dosing. To the extent necessary for completion, the synthesis of the components and dosages described in the patents or CAS documents referenced in the Technology Description portion of this document are expressly incorporated by reference

Desirably, when reboxetine is selected as the active agent, the daily dose contains from about 0.1mg. to about 10 mg. More preferably, each dose of the component contains about 0.5 to about 8 mg of the active ingredient, and even more preferably, each dose contains from about 0.5 to about 5 mg of the active ingredient. This dosage form permits the full daily dosage to be administered in one or two oral doses. This will allow for final formulations containing 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, or 2.5 mg of active. More than once daily or twice daily administrations (e.g., 3, 4, 5 or 6 administrations per day) are also expressly contemplated herein.

The average daily adult dosage of the other norepinephrine reuptake inhibitors is as follows. The dosages expressly include all numerical values, whole or fractional, within the stated range. Pediatric dosages may be less.

Component	Average Daily Dosage (mg/day/patient)
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Tandamine	7.5 to 3750
Pirandamine	7.5 to 3750
Ciclazindol	5 to 500
Fluparoxan	.75 to 750
Lortalamine	1 to 200
Talsupram	1 to 3750
Talopram	1 to 3750
Prindamine	1 to 3750
Nomifensine	1 to 80
Viloxazine	1 to 3750
Tomoxetine	1 to 200
Duloxetine	5 to 500
Venlafaxine	2 to 200
Milnacipran	7.5 to 75

The second component comprises one or more antimuscarinic agents. Examples of such agents include tolterodine, propiverine, oxybutynin, trospium, darifenacin, temiverine and ipratropium. Particularly preferred is tolterodine.

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The chemical name of tolterodine is Phenol, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methyl-, (R)-, including its pharmaceutically active salts, such as those described above with respect to the first active component and its active metabolites that are produced *in vivo*. Synthesis of tolterodine is disclosed in U.S. Patent No. 5,382,600. To the extent necessary for completion, this patent is expressly incorporated by reference. This compound is particularly useful as an anticholinergic agent, and more specifically for the treatment of incontinence.

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As is well known, the dosage and administrative regimen (i.e., one, two, three or more administrations per day) of the second component depends on the factors referred to in connection with the dosage selection of the first component. To the extent necessary for completion, the synthesis of the components and dosages described in the patents or CAS documents referenced in the Technology Description portion of this document are expressly incorporated by reference. The average adult daily dosage of the second

15

component is from about 0.05 mg to about 5 mg per kilogram of body weight, administered in one or more doses, e.g. containing from about 0.05 to about 250 mg each. The dosages expressly include all numerical values, whole or fractional, within the stated range. Pediatric dosages may be less.

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Compositions of the present invention can conveniently be administered in a pharmaceutical composition containing the active components in combination with a suitable excipient. Such pharmaceutical compositions can be prepared by methods and contain excipients which are well known in the art. A generally recognized compendium of such methods and ingredients is Remington's Pharmaceutical Sciences by E.W. Martin (Mark Publ. Co., 15th Ed., 1975). To the extent necessary for completion, this reference is hereby incorporated by reference. The compositions of the present invention can be administered parenterally (for example, by intravenous, intraperitoneal, subcutaneous or intramuscular injection), topically, orally, intranasally, intravaginally, or rectally, with oral administration being particularly preferred.

For oral therapeutic administration, the inventive composition may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums, foods and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 0.1 to about 100% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. The above listing is merely representative and one skilled in the art could envision other binders, excipients, sweetening agents and

the like. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules
5 may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In,
10 addition, the active components may be incorporated into sustained-release preparations and devices including, but not limited to, those relying on osmotic pressures to obtain a desired release profile. Once daily formulations for each of the active components are specifically included.

15 The inventive composition, containing the two active components, may be administered in the same physical form or concomitantly according to the above-described dosages and in the above-described delivery vehicles. The dosages for each active component can be measured separately and can be given as a single combined dose or given separately. They may be given at the same or at different times as long
20 as both actives are in the patient at one time over a 24-hour period. Concomitant or concurrent administration means the patient takes one drug within about 5 minutes of taking the other drug. Because the goal is to provide rapid symptomatic relief to the patient, in most cases when treatment is started the two drugs would be administered to the patient close in time and typically concomitantly; thereafter, the timing of each
25 drug's administration may not be as important.

The inventive composition is used to treat incontinence or any of the diseases or disorders of the central nervous system. Such diseases and disorders are defined in The Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) (American
30 Psychiatric Association (1995)). To the extent necessary for completion, the contents of this reference and all of the defined diseases or disorders are expressly incorporated by reference. Also considered is the treatment of incontinence of any type. Representative diseases or disorders include, but are not limited to the following:

obesity, depression, schizophrenia, a stress related disease (e.g. general anxiety disorder), panic disorder, a phobia, obsessive compulsive disorder, post-traumatic-stress syndrome, immune system depression, incontinence, a stress induced problem with the urinary, gastrointestinal or cardiovascular system (e.g., stress incontinence),
5 neurodegenerative disorders, autism, chemotherapy-induced vomiting, hypertension, migraine headaches, cluster headaches, sexual dysfunction in a mammal (e.g. a human), addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to general medical conditions, attention-deficit hyperactivity disorder,
10 bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, an inhalation disorder, an intoxication disorder, a movement disorder (e.g., Tourette's syndrome), oppositional defiant disorder, a pain disorder, peripheral neuropathy, post-traumatic stress disorder,
15 premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, a specific developmental disorder, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome. Treatment of the above diseases or disorders is accomplished by delivering a therapeutically effective amount of the inventive composition to a mammal. In most cases this will be a human being, but treatment of
20 food animals (e.g., livestock and poultry) and companion animals (e.g., dogs, cats and horses) is expressly covered herein.

In particular, the inventive composition is to be used in the treatment of incontinence (i.e., stress incontinence, genuine stress incontinence, and mixed incontinence). Stress
25 urinary incontinence is a symptom describing involuntary loss of urine on carrying out any activity that raises intra-abdominal pressure such as coughing or sneezing. Stress incontinence is also a clinical sign, that is the observation by a care giver of a jet of urine escaping from the urethral meatus (opening) when the patient coughs or strains. Genuine Stress Incontinence (urge incontinence) is the pathological diagnosis of an
30 incompetent urethral sphincter as diagnosed by Urodynamic testing. Mixed incontinence is stress incontinence in combination with urge incontinence. The latter is a part of the symptom complex of the Overactive Bladder. Retention may be due to outflow obstruction (e.g., high urethral pressure), poor detrusor (bladder muscle)

contractility or lack of coordination between detrusor contraction and urethral relaxation. The inventive drug combination can be used in connection with stress incontinence, urge incontinence or mixed incontinence.

- 5 The novel composition is expected to provide rapid relief to those suffering from the above diseases or disorders with a minimal amount of deleterious side effects.

The invention is described in greater detail by the following non-limiting example.

10

Example 1

A pharmaceutical composition is prepared by combining reboxetine in either its racemic or (S,S) enantiomeric form with tolterodine in a pharmaceutically acceptable carrier. The composition contains respective amounts of reboxetine and tolterodine
15 to deliver on a daily basis between about 0.1 mg to about 10 mg reboxetine and between about 0.05 mg to about 4 mg of tolterodine per kilogram of patient body weight (for example, 3 mg to 240 mg tolterodine for a person weighing 60 kg). The composition is administered to a patient for the treatment of incontinence, and particularly stress incontinence, urge incontinence or mixed incontinence.

20

Example 2

A first pharmaceutical composition is prepared by combining reboxetine in either its racemic or +(S,S) enantiomeric form in a pharmaceutically acceptable carrier such
25 that it can deliver between about 0.1 mg to about 10 mg reboxetine on a daily basis. A second pharmaceutical composition is prepared by combining tolterodine in a pharmaceutically acceptable carrier such that it can deliver between about 0.05 mg to about 4 mg of tolterodine per kilogram of patient body weight on a daily basis. The first composition is administered to a patient suffering from one or more forms of
30 incontinence once, twice, three times, four times or six times daily such that the daily dosage is between about 0.1 to about 10 mg. The second composition is administered to the same patient at the same time as the administration of the first composition or any time within 24 hours of the administration of the first composition once, twice,

three times, four times or six times daily such that the daily dosage is between about 0.05 mg to about 4 mg of tolterodine per kilogram of patient body weight. Alternatively, the second composition could first be administered, followed by the administration of the first composition as disclosed at the same time, or within 24
5 hours thereof.

Having described the invention in detail and by reference to the preferred embodiments thereof, it will be apparent that modifications and variations are possible without departing from the scope of the appended claims.

10

What is claimed is:

1. A composition comprising:
 - 5 (a) a pharmaceutically effective amount of one or more norepinephrine reuptake inhibitors or a pharmaceutically effective salt thereof; and
 - (b) a pharmaceutically effective amount of one or more antimuscarinic agents or a,
10 pharmaceutically effective salt thereof.
2. The composition according to claim 1 wherein component (a) is selected from the group consisting of tandamine, pirandamine, ciclazindol, fluparoxan, lortalamine, talsupram, talopram, prindamine, nomifensine, viloxazine, tomoxetine, duloxetine,
15 venlafaxine, milnacipran and reboxetine and mixtures thereof and wherein component (b) is selected from the group consisting of tolterodine, propiverine, oxybutynin, trospium, darifenacin, temiverine and ipratropium and mixtures thereof.
3. The composition according to claim 2 wherein component (a) is reboxetine in
20 either its racemic or +(S,S) enantiomeric form and component (b) is tolterodine, its active metabolites or mixtures thereof.
4. The composition according to claim 3 containing between about 0.1 mg to about 10 mg reboxetine and between about 0.05 mg to about 4 mg of tolterodine per
25 kilogram of patient body weight.
5. The composition according to claim 1 wherein component (a) and component (b) are maintained in the same delivery vehicle.
- 30 6. The composition according to claim 1 wherein component (a) and component (b) are maintained in different delivery vehicles.

7. A method for treating incontinence or a disease or disorder of the central nervous system in a mammal comprising administering to said mammal a pharmaceutically effective amount of a composition comprising:
- 5 (a) a pharmaceutically effective amount of one or more norepinephrine reuptake inhibitors or a pharmaceutically effective salt thereof; and
- (b) a pharmaceutically effective amount of one or more antimuscarinic agents or a pharmaceutically effective salt thereof.
- 10
8. The method according to claim 7 wherein said disease or disorder is selected from the group consisting of obesity, depression, schizophrenia, a stress related disease (e.g. general anxiety disorder), panic disorder, a phobia, obsessive compulsive disorder, post-traumatic-stress syndrome, immune system depression, incontinence, a stress
- 15 induced problem with the urinary, gastrointestinal or cardiovascular system, neurodegenerative disorders, autism, chemotherapy-induced vomiting, hypertension, migraine headaches, cluster headaches, sexual dysfunction in a mammal, addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to
- 20 general medical conditions, attention-deficit hyperactivity disorder, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, an inhalation disorder, an intoxication disorder, a movement disorder, oppositional defiant disorder, a pain disorder, peripheral neuropathy, post-traumatic
- 25 stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal affective disorder, a sleep disorder, a specific developmental disorder, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome.
9. The method of claim 7 wherein said composition is administered rectally,
- 30 topically, orally, sublingually, intranasally, transdermally or parenterally.
10. The method of claim 7 wherein component (a) and component (b) of said composition are simultaneously administered.

11. The method of claim 7 wherein component (a) and component (b) of said composition are concomitantly administered.

5 12. The method according to claim 7 wherein said disease or disorder comprises incontinence.

13. The method according to claim 12 wherein said incontinence is stress incontinence, genuine stress incontinence or mixed incontinence.

10

14. The method according to claim 13 wherein component (a) of said composition comprises reboxetine in its racemic or enantiomeric form and component (b) of said composition comprises tolterodine, its active metabolites or mixtures thereof.

15 15. The method according to claim 12 wherein said composition contains between about 0.1 mg to about 10 mg reboxetine and between about 0.05 mg to about 4 mg of tolterodine per kilogram of patient body weight.

16. A composition consisting essentially of:

20

(a) a pharmaceutically effective amount of reboxetine in its racemic or enantiomeric form or a pharmaceutically effective salt thereof; and

(b) a pharmaceutically effective amount of tolterodine, its active metabolites or combinations thereof or a pharmaceutically effective salt thereof;

25

wherein components (a) and (b) are maintained in the same or in different delivery vehicles.

30 17. The use of a composition comprising:

(a) a pharmaceutically effective amount of one or more norepinephrine reuptake inhibitors or a pharmaceutically effective salt thereof; and

(b) a pharmaceutically effective amount of one or more antimuscarinic agents or a pharmaceutically effective salt thereof to prepare a medicament for treating or preventing incontinence or diseases or disorders of the central nervous system.

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18. The use according to claim 17 wherein component (a) comprises reboxetine in its racemic or enantiomeric form and component (b) comprises tolterodine, its active metabolites or mixtures thereof.

10 19. A composition comprising:

(a) a pharmaceutically effective amount of one or more norepinephrine reuptake inhibitors or a pharmaceutically effective salt thereof; and

15 (b) a pharmaceutically effective amount of one or more antimuscarinic agents or a pharmaceutically effective salt thereof for use as a medicament.

20. A composition comprising:

20 (a) a pharmaceutically effective amount of one or more norepinephrine reuptake inhibitors selected from the group consisting of tandamine, pirandamine, ciclazindol, fluparoxan, lortalamine, talsupram, talopram, prindamine, nomifensine, viloxazine, tomoxetine, duloxetine, venlafaxine, milnacipran and reboxetine and mixtures thereof or a pharmaceutically effective salt thereof; and

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(b) a pharmaceutically effective amount of one or more antimuscarinic agents selected from the group consisting of tolterodine, propiverine, oxybutynin, trospium, darifenacin, temiverine and ipratropium and mixtures thereof or a pharmaceutically effective salt thereof;

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21. The composition according to claim 20 wherein component (a) is reboxetine in either its racemic or +(S,S) enantiomeric form and component (b) is darifenacin.

22. The composition according to claim 20 wherein component (a) is reboxetine in either its racemic or +(S,S) enantiomeric form and component (b) is trospium.
23. The composition according to claim 20 wherein component (a) is reboxetine in either its racemic or +(S,S) enantiomeric form and component (b) is ipratropium.
24. The composition according to claim 20 wherein component (a) is duloxetine.
25. The composition according to claim 23 wherein component (b) is selected from the group consisting of tolterodine, darifenacin, trospium, ipratropium and mixtures thereof.
26. The composition according to claim 25 containing between about 1 mg to about 200 mg duloxetine and between about 0.05 mg to about 5 mg of component (b) per kilogram of patient body weight.
27. The composition according to claim 20 wherein component (a) and component (b) are maintained in the same delivery vehicle.
28. The composition according to claim 20 wherein component (a) and component (b) are maintained in different delivery vehicles.
29. A method for treating incontinence or a disease or disorder of the central nervous system in a mammal comprising administering to said mammal a pharmaceutically effective amount of a composition comprising:
- (a) a pharmaceutically effective amount of one or more norepinephrine reuptake inhibitors tandamine, pirandamine, ciclazindol, fluparoxan, lortalamine, talupram, talopram, prindamine, nomifensine, viloxazine, tomoxetine, duloxetine, venlafaxine, milnacipran and reboxetine and mixtures thereof or a pharmaceutically effective salt thereof; and

(b) a pharmaceutically effective amount of one or more antimuscarinic agents selected from the group consisting of tolterodine, propiverine, oxybutynin, trospium, darifenacin, temiverine and ipratropium and mixtures thereof or a pharmaceutically effective salt thereof.

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30. The method according to claim 29 wherein said disease or disorder is selected from the group consisting of obesity, depression, schizophrenia, a stress related disease (e.g. general anxiety disorder), panic disorder, a phobia, obsessive compulsive disorder, post-traumatic-stress syndrome, immune system depression, incontinence, a stress induced problem with the urinary, gastrointestinal or cardiovascular system, neurodegenerative disorders, autism, chemotherapy-induced vomiting, hypertension, migraine headaches, cluster headaches, sexual dysfunction in a mammal, addictive disorder and withdrawal syndrome, an adjustment disorder, an age-associated learning and mental disorder, anorexia nervosa, apathy, an attention-deficit disorder due to
10 general medical conditions, attention-deficit hyperactivity disorder, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, conduct disorder, cyclothymic disorder, dysthymic disorder, fibromyalgia and other somatoform disorders, generalized anxiety disorder, an inhalation disorder, an intoxication disorder, a movement disorder, oppositional defiant disorder, a pain disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder, seasonal
15 affective disorder, a sleep disorder, a specific developmental disorder, and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome.

31. The method of claim 30 wherein component (a) and component (b) of said
25 composition are simultaneously administered.

32. The method of claim 30 wherein component (a) and component (b) of said composition are concomitantly administered.

30 33. The method according to claim 30 wherein said disease or disorder comprises incontinence.

34. The method according to claim 33 wherein said incontinence is stress incontinence, genuine stress incontinence or mixed incontinence.

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Reboxetine: a review of antidepressant tolerability

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The tolerability of reboxetine was evaluated in 2613 adult (aged 18–65 years) or elderly (aged > 65 years) patients with depressive illness treated with reboxetine, comparator agents or placebo, who entered both short- and long-term, controlled and uncontrolled clinical trials. The reboxetine adverse-event profile in acute depression was established by comparison with placebo in 746 patients. Overall, 69% of 373 patients treated with reboxetine experienced adverse events compared with 57% of 373 patients in the placebo group. The majority of adverse events were moderate in severity, and discontinuation because of adverse events was low and comparable in both the reboxetine (8%) and the placebo (7.5%) group. When compared with imipramine, reboxetine was better tolerated. Most side-effects were less common in the reboxetine than the imipramine cohort, and fewer patients receiving reboxetine (10% in adult patients; 11% in elderly patients) discontinued treatment because of adverse events than those receiving imipramine (14% in adult patients; 16% in elderly patients). Compared with fluoxetine, the total frequency of adverse events was similar in reboxetine-treated patients (67%) and fluoxetine-treated patients (65%). In the fluoxetine group, 7% discontinued because of adverse events compared to 12% in the reboxetine group and 12% in the corresponding placebo group. In a 12-month placebo-controlled study, discontinuation because of adverse events in both groups was low (reboxetine 4%; placebo 1%), and the total frequency of adverse events was only marginally higher with reboxetine (28%) than with placebo (23%). Overall, no consistent changes were found in laboratory tests or electrocardiogram recordings and there was no indication of withdrawal symptoms upon abrupt reboxetine discontinuation. Reboxetine, a novel selective noradrenaline reuptake inhibitor, is well tolerated by adults and the elderly during short- and long-term treatment for depression.

Key words: desipramine; elderly; fluoxetine; imipramine; long-term treatment; reboxetine; tolerability

Introduction

The tolerability profile of reboxetine was evaluated in 2613 patients with depressive disorders who were treated with reboxetine, desipramine, imipramine, fluoxetine, or placebo in clinical trials.

In this overall analysis, the results obtained in short-term studies and in the short-term run-in phase of the long-term studies are discussed separately from those obtained in the maintenance phase of the long-term studies. Results in adult patients (aged 18–65 years) are also discussed separately from those obtained in elderly patients (aged > 65 years).

Short-term treatment: adult patients

The adult (18–65 years) population in the short-term studies included 1247 patients ($n=832$ females; $n=424$ males) who were treated with reboxetine and 913 patients who were treated with placebo ($n=373$), imipramine ($n=241$), fluoxetine ($n=216$), or desipramine ($n=83$).

In the controlled studies, the maximum administered dose of reboxetine was 8 mg/day in 74% of patients, lower than 8 mg/day in 1% of patients, and higher than 8 mg/day (i.e. 10 mg/day or higher in case of overdose) in 25% of patients.

Placebo controlled studies: adverse events

Data for 373 patients treated with reboxetine and for the 373 patients treated with placebo are included in the safety evaluation from the placebo-controlled studies. Overall, 69% of the reboxetine-treated patients (95% CI 64–74) and 57% of the placebo-treated patients (95% CI 52–63) reported adverse events.

Among the most frequently reported adverse events (i.e. events reported by $\geq 2\%$ of patients who were treated with reboxetine), the following events had a statistically significant higher risk of development with reboxetine than with placebo (Kaplan–Meier analysis): vertigo (2% vs. 0%); tachycardia (5% vs. 2%); impotence (5% vs. 0% of male patients); urinary hesitancy/retention (5% vs. 2% of which retention constituted 2% and 1%, respectively); insomnia (14% vs. 5%); increased sweating (14% vs. 7%); constipation (17% vs. 8%); dry mouth (27% vs. 16%) (Fig. 1). Acute urinary retention resulting in

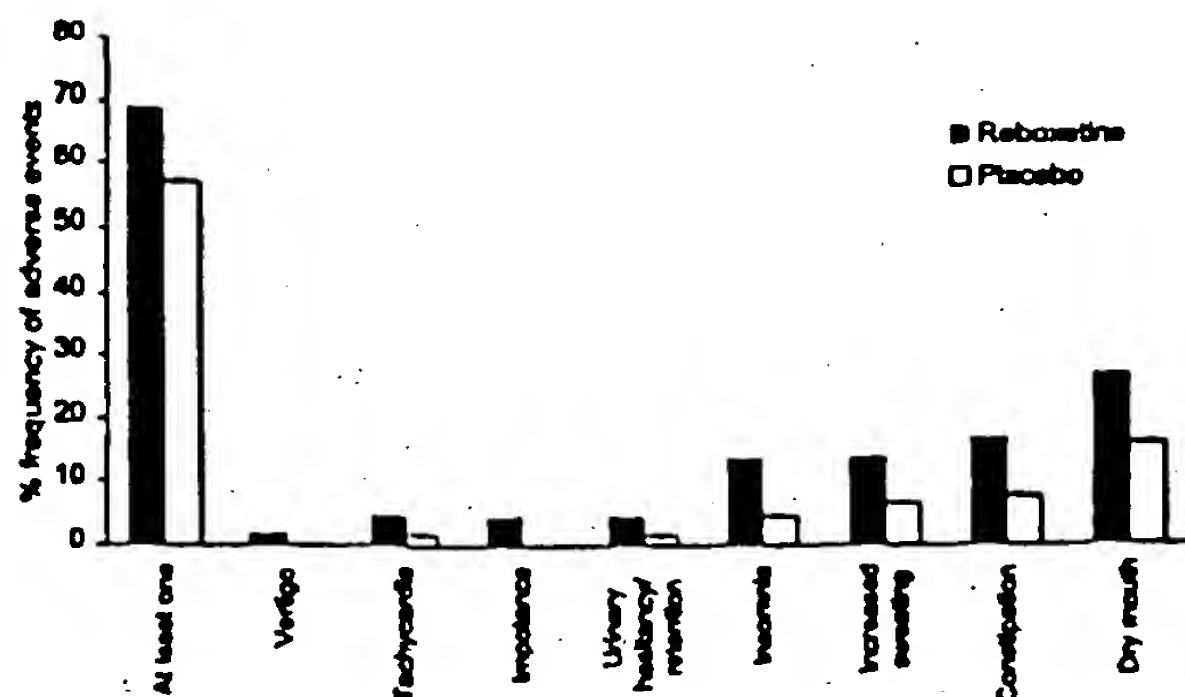


Figure 1 Frequency of adverse events with a statistically significantly higher risk of development on reboxetine than on placebo (Kaplan-Meier analysis)

catheterization was rare (<1%). Interestingly, selective serotonin reuptake inhibitor-type side-effects such as nausea (8% vs. 7%) and anxiety/agitation (6% vs. 7%) were no more common in those patients treated with reboxetine than in those receiving placebo.

The majority of adverse events in the reboxetine group were moderate in severity. No relevant gender- or age-related differences were apparent.

Except for a few events (impotence and decreased libido for which 44% and 38% of the total events, respectively, emerged at high doses), there was little indication of an increased frequency or severity of adverse events in patients who received doses of reboxetine higher than 8 mg/day. Discontinuation because of adverse events was low and comparable in both the reboxetine and placebo groups; 8% and 7.5%, respectively.

Active treatment-controlled studies: adverse events

Imipramine-controlled studies

Two hundred and forty-two patients ($n = 154$ females; $n = 88$ males) received reboxetine and 241 patients ($n = 160$ females; $n = 81$ males) received imipramine. Reboxetine or imipramine (150–200 mg/day) were administered twice daily. Seventy-three per cent of reboxetine-treated (95% CI 67–79) and 76% of imipramine-treated patients (95% CI 71–82) reported adverse events. The overall frequency of adverse events was slightly lower in the reboxetine group than in the imipramine group for both male and female patients.

The frequency of adverse events with a cumulative risk of occurrence was significantly different in the two groups. The following adverse events had a significantly higher risk of development on imipramine than reboxetine: somnolence (7% vs. 2%); tremor (15% vs. 4%); hypotension and related symptoms (20% vs. 10%); dry mouth (42% vs. 26%). Significant differences were always in favour of reboxetine (Fig. 2).

No adverse events were significantly more likely with reboxetine than with imipramine. No relevant gender- or age-related differences were apparent.

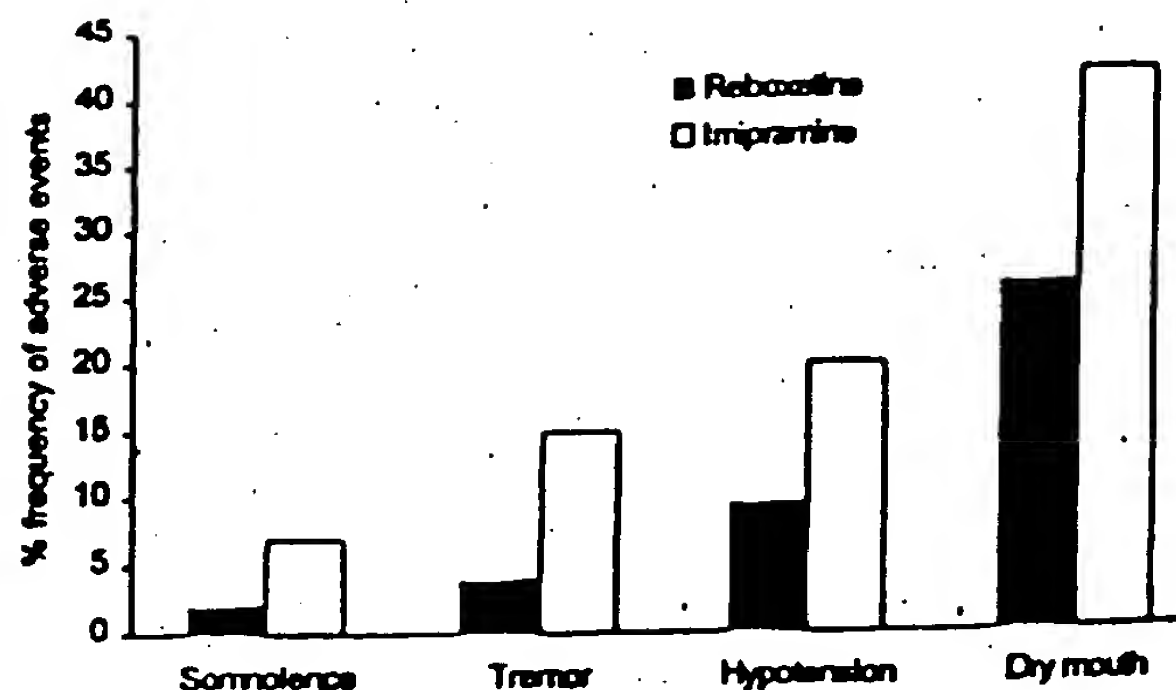


Figure 2 Frequency of adverse events with a statistically significantly higher risk of development on imipramine than on reboxetine (Kaplan-Meier analysis)

Ten per cent and 14% of reboxetine- and imipramine-treated patients, respectively, withdrew because of adverse events.

Fluoxetine-controlled studies

Two hundred and five patients ($n = 142$ females; $n = 63$ males) received reboxetine and 216 patients ($n = 147$ females; $n = 69$ males) received fluoxetine in the fluoxetine-controlled studies. Sixty-seven per cent of reboxetine-treated (95% CI 60–73) and 65% of fluoxetine-treated patients (95% CI 59–72) reported adverse events.

Among the most frequently reported adverse events (i.e. events reported by $\geq 2\%$ of patients who were treated with reboxetine), a statistically significantly higher risk of development on reboxetine than on fluoxetine (Kaplan-Meier analysis) was found for: flushing (3% vs. 0.5%), urinary hesitancy/retention (6% vs. 0.5%, of which retention constituted 1.5% and 0%, respectively), paraesthesia (6% vs. 1%), hypotension and related symptoms (14% vs. 6%), constipation (18% vs. 5%), and dry mouth (28% vs. 7%) [Fig. 3(a)]. A significantly higher risk of development of adverse events on fluoxetine was found for somnolence (5% vs. 1%), diarrhoea (8% vs. 2%), and nausea and related symptoms (26% vs. 16%) [Fig. 3(b)].

Twelve per cent of reboxetine-treated patients discontinued because of adverse events compared with 7% of fluoxetine-treated patients.

In the placebo-controlled fluoxetine comparator study, 12% of patients in both the reboxetine and the placebo groups discontinued because of adverse events.

Desipramine-controlled study

The adverse-event profile of reboxetine relative to that of desipramine was determined in one study. Autonomic adverse events occurred more frequently in the desipramine group than in either the reboxetine or the placebo group, in particular: dry mouth (45% of desipramine-treated patients vs. 26% of the reboxetine-treated patients and 21% of the placebo-treated patients), increased sweating (28% of the desipramine-treated patients vs. 18% and 22% of the reboxetine- and placebo-treated patients, respectively), and blurred vision (17% of the desipramine-treated patients vs. 4% of the reboxetine- and

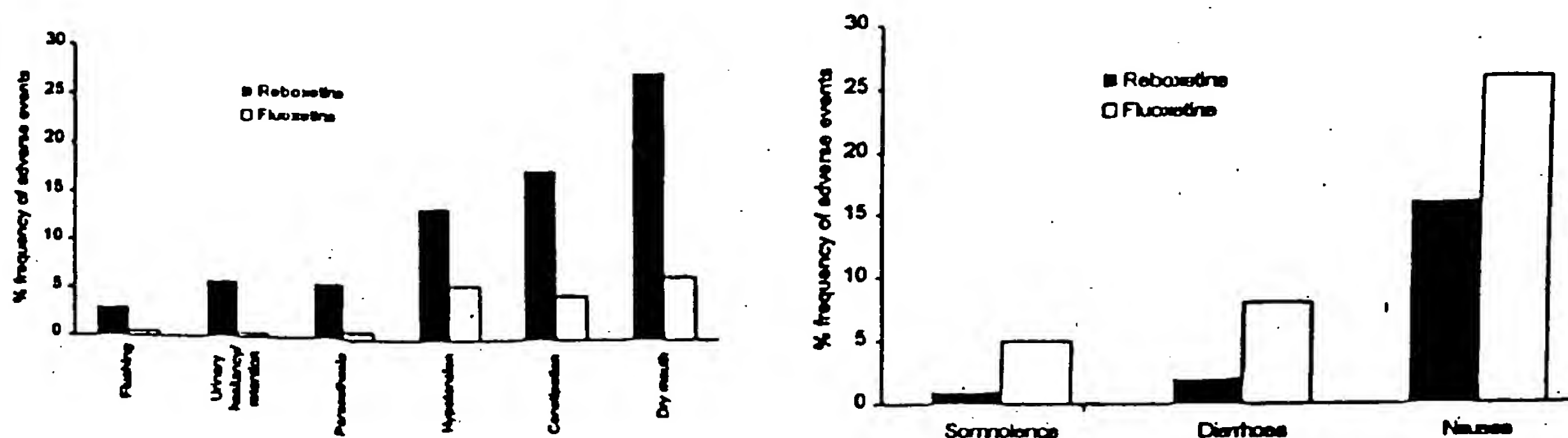


Figure 3 (a) Frequency of adverse events with a statistically significantly higher risk of development on reboxetine than on fluoxetine. (b) Frequency of adverse events with a statistically significantly higher risk of development on fluoxetine than on reboxetine

placebo-treated patients, respectively). Urinary hesitancy/retention occurred in 12% of the reboxetine-treated patients versus 4% and 1% of the desipramine- and placebo-treated patients, respectively. The frequency of hypotension and tachycardia in the reboxetine group (6% and 12%, respectively) was within the range reported for the placebo group (8% for each event). Both hypotension and tachycardia were reported somewhat more frequently in the desipramine group (13% and 19%, respectively) than in the placebo group.

Vital signs, laboratory tests, and electrocardiograms
The patient population includes 2160 patients ($n=1384$ females; $n=776$ males) who received reboxetine, placebo, imipramine, fluoxetine, or desipramine.

No important trends were apparent in mean or median blood pressure values or in the changes in blood pressure in the adult population in any treatment group. During treatment, clinically relevant blood pressure changes occurred evenly in all treatment groups, however, a greater percentage of patients in the imipramine group than in the other groups had at least one clinically relevant decrease in standing blood pressure.

Haematology and blood chemistry tests provided no evidence of any clinically relevant toxic effect of short-term treatment with reboxetine in adult patients.

In the 1008 adult reboxetine-treated patients who had an electrocardiogram (ECG) recording at baseline and at least one follow-up evaluation, no modifications were observed in the frequency of patients who had at least one treatment-emergent abnormality. In the reboxetine group, 14% of patients had ECG abnormalities at baseline and 14% and 15% had abnormalities after 4 and 8 weeks of treatment, respectively. In the placebo group, 9% of 309 patients had abnormalities at baseline and 10% and 14% had abnormalities after 4 and 8 weeks of treatment, respectively. No relevant changes were observed in the 191 fluoxetine-treated patients, but slightly increased frequencies were apparent in the 189 imipramine-treated patients (from 12% at baseline to 19% and 16% after 4 and 8 weeks of treatment, respectively).

Short-term treatment: elderly patients

One study compared the efficacy and safety of reboxetine and imipramine for short-term treatment of patients with major depressive disorder or dysthymia.

Adverse events

One hundred and seventy-six patients received reboxetine and 171 patients received imipramine. Sixty-eight per cent of reboxetine-treated (95% CI 61–75) and 71% of imipramine-treated patients (95% CI 64–78) reported adverse events. No gender-related differences were observed in the overall frequency of adverse events in either treatment group.

The frequency of the majority of adverse events was very similar in the two treatment groups. Urinary hesitancy/retention was reported by 4% of patients in the reboxetine group and by 6% of patients in the imipramine group; headache/migraine was reported by 6% and 5% of patients in the reboxetine and imipramine groups, respectively. Increased sweating was reported by 9% of patients in each group; nausea was reported by 11% of patients in the reboxetine group and 10% of patients in the imipramine group. Constipation was reported in 18% of patients in each group, and dry mouth was reported by 22% of patients in the reboxetine group and 23% of patients in the imipramine group. The cumulative risk was significantly higher on imipramine for hypotension and related symptoms (frequency of 16% vs. 7%).

The frequency of cardiovascular adverse events was greater in the imipramine group than in the reboxetine group. In patients who were treated with reboxetine, the presence of cardiovascular disorders at baseline did not seem to facilitate the emergence of cardiovascular adverse events and, in particular, the emergence of hypotension and related symptoms. However, patients in the imipramine group experienced treatment-emergent cardiovascular adverse events and, in particular, the emergence of hypotension and related symptoms more frequently when they were affected by cardiovascular disorders at baseline (26% and 21% for cardiovascular events and for hypotension and related symptoms, respectively) than

when they were not affected by cardiovascular disorders at baseline (17% and 12%, respectively).

Adverse events determined treatment discontinuation in 11% and 16% of reboxetine- and imipramine-treated patients, respectively.

Vital signs, laboratory tests and electrocardiograms
No important trends were apparent in mean or median blood pressure, heart rate or in changes in blood pressure or heart rate in elderly patients in either treatment group. The absolute frequency of clinically relevant changes in blood pressure was mainly apparent for diastolic blood pressure in both the reboxetine and imipramine groups. The maximum difference between reboxetine and imipramine was observed in the absolute frequency of clinically relevant decreases in standing diastolic blood pressure, which was greater in the imipramine group (22%) than in the reboxetine group (13%). In the majority of these patients, the relevant decrease occurred occasionally (15% of evaluated patients in the imipramine group and 5% in the reboxetine group). Increases in heart rate to values of 100 beats/min or higher occurred at least once in a greater proportion of patients in the reboxetine group than in the imipramine group, with the maximum difference observed in standing heart rate (12% vs. 6%, respectively).

Haematology and blood chemistry tests provided no evidence of any clinically relevant toxic effects of short-term treatment with reboxetine in elderly patients.

Tachycardia and occasional atrial and ventricular ectopic beats accounted for the rhythm disorders that emerged during reboxetine treatment. Similar disorders were also seen with imipramine treatment. These abnormalities emerged in 13% of the reboxetine group and 6% of the imipramine group, the difference being accounted for by sinus tachycardia and occasional atrial ectopic beats. Treatment-emergent abnormalities related to conduction disorders were observed in 6% of the reboxetine-treated group (almost exclusively left anterior hemiblock) and in 4% of imipramine-treated patients (most commonly right bundle branch block).

Long-term treatment: adult patients

Two hundred and eighty-three patients received reboxetine for up to 12 months in one placebo-controlled and in one uncontrolled study. Seventy-five per cent of patients in these studies were female.

In both studies a dose of 8 mg/day was given in almost all cases.

Of the 143 and 140 patients who were treated with reboxetine or placebo in the controlled study, 71% and 65%, respectively, received the treatment for at least 6 months; 56% and 47%, respectively, were treated for approximately 12 months.

Adverse events

One hundred and forty-three patients treated with reboxetine and 140 patients treated with placebo were included in the adverse-event analysis. The total frequency of adverse events was only marginally higher with reboxetine (28%) than with placebo (23%). The adverse events reported more frequently

for reboxetine-treated patients than for placebo-treated patients during the long-term, double-blind phase of the study were as follows: rash (2% vs. 0%), hypertension (3% vs. 1%), urinary hesitancy/retention (4% vs. 1%), and constipation (8% vs. 4%). The cumulative risk of developing the first adverse event, as well as individual events, analysed according to the Kaplan-Meier method, was similar in both reboxetine- and placebo-treated patients.

Between-gender differences in the frequency of urinary hesitancy/retention, was primarily reported by male patients (14% and 2% of the males in the reboxetine and placebo groups, respectively). Urinary hesitancy/retention in male patients was the only relevant event that was reported more frequently in the long-term placebo-controlled study than in the short-term placebo-controlled studies (10%).

Four per cent of patients in the reboxetine group discontinued because of adverse events compared with 1% in the placebo group.

Vital signs, laboratory tests and electrocardiograms

No trend towards modification in systolic or diastolic blood pressure was apparent during long-term treatment. Clinically relevant changes in systolic and diastolic blood pressure occurred at a similar frequency in the reboxetine and placebo groups. Orthostatic hypotension was reported at least once during long-term treatment with a similar frequency in the reboxetine and placebo groups (4% each).

There was a trend towards a small increase in heart rate in the reboxetine group (not exceeding 5 beats/min) and towards decreased values in the placebo group (not exceeding 5 beats/min). Relevant increases in heart rate to values of 100 beats/min or higher occurred at least once during the long-term phase in a slightly greater proportion of patients in the reboxetine group than in the placebo group, with the maximal difference between groups observed in standing heart rate (23% vs. 17% of the evaluated patients in the reboxetine and placebo groups, respectively).

Haematology and blood chemistry tests provided no evidence of any clinically relevant toxic effects of long-term treatment with reboxetine.

At the last assessment of the long-term treatment period, 10% of reboxetine-treated patients and 4% of placebo-treated patients with normal tracings at baseline had at least one abnormality. Among patients who had at least one abnormality at baseline, 67% in the reboxetine group and 59% in the placebo group had reportedly normal findings at the last assessment. During long-term treatment, no trend towards an increased frequency in any of the abnormalities were reported in either treatment group.

At the last assessment of the long-term treatment period, the proportion of treatment-emergent ECG abnormalities was low and generally similar in both groups. However, rhythm disorders occurred more frequently in the reboxetine group (6%) than in the placebo group (1%). Among these abnormalities, the most common was sinus tachycardia, which was present in 5% of patients in the reboxetine group and in none of the patients in the placebo group. However, the proportion of treatment-emergent abnormalities in rhythm disorders, sinus tachycardia, and all other disorders in the

reboxetine group was far lower than the proportion of normalized findings.

Long-term treatment: elderly patients

Preliminary analysis of data from 40 elderly patients who received long-term reboxetine treatment in an uncontrolled study has been carried out.

The adverse events newly emerged on long-term reboxetine treatment were, in the majority of the cases, similar to those apparent on short-term treatment, but far less in frequency. Both overall frequency of adverse events (35%) and discontinuation because of adverse events (10%) were similar to that observed in the overall reboxetine-treated population (42% and 8%, respectively).

Serious adverse events: adult patients

Eleven serious adverse events were reported for 11 (0.9%) reboxetine-treated patients; six serious adverse events were reported for six (2.5%) of the imipramine-treated patients; two serious adverse events were reported for two (0.9%) of the fluoxetine-treated patients; and four serious adverse events were reported for four (0.8%) of the placebo-treated patients. The most frequent serious adverse events were related to psychiatric disorders (six reboxetine-treated patients), central nervous system (CNS) disorders (two reboxetine-treated patients), cardiovascular system disorders (one reboxetine-treated patient), and other body systems disorders (two reboxetine-treated patients).

The frequency of suicide or attempted suicide was 0.3% in the reboxetine group, which was lower than in the groups treated with placebo (0.6%), fluoxetine (0.5%) and imipramine (1.0%).

The seizure rate with reboxetine was 0.13%, which was lower than that with imipramine (0.24%).

All but one of the 11 serious adverse events were reported during short-term treatment. The only event reported during long-term treatment was attempted suicide by overdose of multiple drugs in a reboxetine-treated patient.

Serious adverse events: elderly patients

Seven serious adverse events were reported for seven (2.7%) reboxetine-treated patients, and 14 serious adverse events were reported for 13 (7.6%) imipramine-treated patients. No serious adverse events were reported in the placebo-treated patients.

The most frequent serious adverse events were related to cardiovascular system disorders, psychiatric disorders, CNS disorders, and other body systems disorders. Death occurred in 1.2% of reboxetine-treated elderly patients versus 1.8% (excluding one suicide) of imipramine-treated elderly patients.

In conclusion, serious adverse events were reported with limited frequency in reboxetine-treated patients. Overall, the reboxetine-associated frequency was similar to the placebo-associated frequency in adult patients, and lower than the

imipramine-associated frequency in both the adult and the elderly population.

Dropouts caused by adverse events

Two patients (0.2%) died (suicide), while another 96 of the 1247 adult patients (8%) discontinued because of adverse events. Events most frequently associated with discontinuation largely overlap those found in the placebo-controlled series, only tachycardia (0.8%) and urinary hesitancy/retention (1%) were reported with a higher frequency.

In elderly patients the analysis focused on the direct reboxetine versus imipramine comparison ($n=256$) where discontinuation because of adverse events was more frequent with imipramine (16%) than with reboxetine (11%).

Signs and symptoms at withdrawal

The proportion of patients who reported signs or symptoms of withdrawal at discontinuation was lower among the reboxetine-treated patients (4% of 143 patients) than among the placebo-treated (6% of 66 patients), imipramine-treated (10% of 71 patients), or fluoxetine-treated (11% of 55 patients) patients. These results indicate that reboxetine is unlikely to induce withdrawal signs or symptoms on abrupt discontinuation.

Conclusions

The tolerability of reboxetine has been evaluated in both the short- and long-term treatment of depression; in adult and elderly patients. Reboxetine has proved to be well tolerated in comparison with placebo with a similar number of discontinuations because of adverse events in the two treatment groups. Few adverse events had a significantly higher risk of development with reboxetine compared with placebo and the majority of adverse events were moderate in severity. Reboxetine was better tolerated than imipramine with an overall frequency of adverse events that was slightly lower. Compared with fluoxetine, reboxetine was equally well tolerated.

During long-term treatment of depression, the frequency of adverse events with reboxetine was similar to that reported in the short-term studies, and less than 5% of patients discontinued treatment because of adverse events in both the reboxetine and placebo treatment groups.

In summary, reboxetine, a new selective noradrenaline reuptake inhibitor, was well tolerated by adults and the elderly during short- and long-term treatment for depression.

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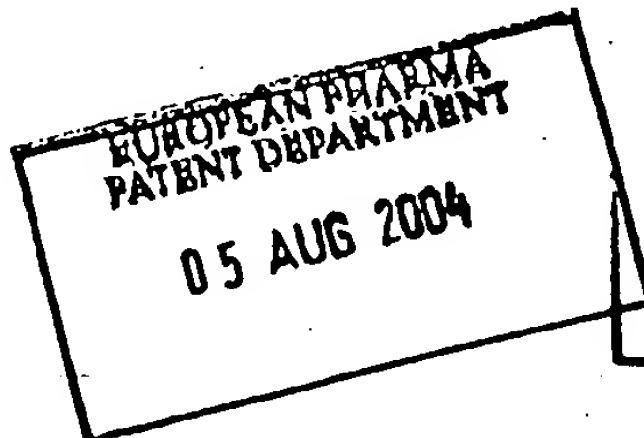
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Anmeldung Nr./Application No./Demande n°/Patent Nr./Patent No./Brevet n°.

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Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire

Pharmacia & Upjohn Company

COMMUNICATION

The European Patent Office herewith transmits as an enclosure the European search report for the above-mentioned European patent application.

If applicable, copies of the documents cited in the European search report are attached.

☒ Additional set(s) of copies of the documents cited in the European search report is (are) enclosed as well.

The following specifications given by the applicant have been approved by the Search Division:

☒ abstract

☐ title

☐ The abstract was modified by the Search Division and the definitive text is attached to this communication.

The following figure will be published together with the abstract:

NONE

FILING	<input checked="" type="checkbox"/>
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RECORDABLE	<input type="checkbox"/>

REFUND OF THE SEARCH FEE

If applicable under Article 10 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.





DOCUMENTS CONSIDERED TO BE RELEVANT					
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Incl.7)		
E	WO 01/62236 A (ROGOSKY KAREN ; UPJOHN CO (US); JORN DEBORAH (US)) 30 August 2001 (2001-08-30) * abstract * * page 6, line 28 - page 7, line 7; claims 1,3,7,8 *	1-7	A61K31/5375 A61P25/06		
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D,A	GB 2 167 407 A (ERBA FARMITALIA) 29 May 1986 (1986-05-29) * abstract * * page 4, line 50 - page 5, line 25; claims; examples 11-13 *	1-7			
A	FRIGERIO E ET AL: "PHARMACOKINETICS OF REBOXETINE ENANTIOMERS IN THE DOG" CHIRALITY, WILEY-LISS, NEW YORK, US, vol. 9, 1997, pages 303-306, XP000991008 ISSN: 0899-0042 * the whole document *	1-7	TECHNICAL FIELDS SEARCHED (Incl.7) A61K A61P		
A	DOSTERT P ET AL: "REVIEW OF THE PHARMACOKINETICS AND METABOLISM OF REBOXETINE, A SELECTIVE NORADRENALINE REUPTAKE INHIBITOR" EUROPEAN NEUROPSYCHOPHARMACOLOGY, ELSEVIER SCIENCE PUBLISHERS BV, AMSTERDAM, NL, vol. 7, no. SUPPL 1, 1997, pages S23-S35, XP000989913 ISSN: 0924-977X * the whole document *	1-7			
The present search report has been drawn up for all claims					
Place of search The Hague		Date of completion of the search 22 July 2004	Examiner Hoff, P		
<table border="0"><tr><td>CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</td><td>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document</td></tr></table>				CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document	T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document
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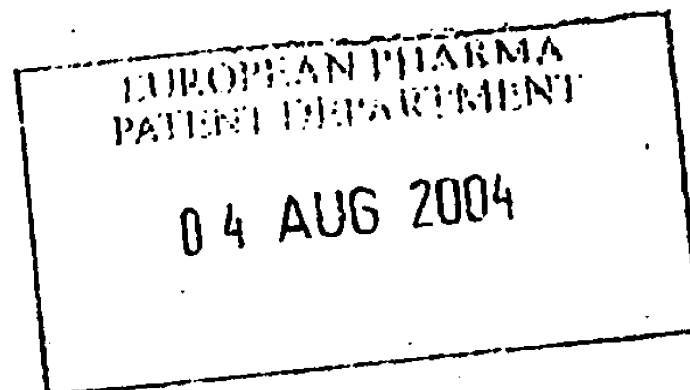
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Datum/Date
04.08.04

Zeichen/Ref./Réf. PC24972-Div.2	Anmeldung Nr./Application No./Demande n°/Patent Nr./Patent No./Brevet n°. 04013382.9-2123-
Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire Pharmacia & Upjohn Company	

COMMUNICATION

The European Patent Office herewith transmits as an enclosure the European search report for the above-mentioned European patent application.

If applicable, copies of the documents cited in the European search report are attached.

☒ Additional set(s) of copies of the documents cited in the European search report is (are) enclosed as well.

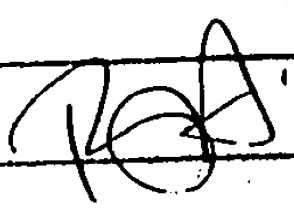
The following specifications given by the applicant have been approved by the Search Division:

☒ abstract ☐ title

☐ The abstract was modified by the Search Division and the definitive text is attached to this communication.

The following figure will be published together with the abstract: NONE

DIARY:-	4.8.04
	4.9.04



REFUND OF THE SEARCH FEE

If applicable under Article 10 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.





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